

COLOR ATLAS OF HUMAN POISONING AND ENVENOMING



JAMES H. DIAZ

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Preface

The field of medical toxicology can be simply divided into animal and human poisonings from animal, plant, or man-made sources. Even more precisely, toxinology is the study of poisoning and envenoming by biological organisms, and toxicology is the study of human poisoning from manmade sources. Living organisms, such as animals, plants, and fungi, produce biological toxins. Man-made toxins, or toxoids, are produced by controlled chemical reactions, often on an industrial scale, designed to produce novel pharmaceuticals, cosmetics, household cleansers, fertilizers, herbicides, pesticides, and other useful and necessary consumer and commercial products. Unfortunately, some biological toxins have already been developed, deployed, and used as bioterror weapons (e.g., ricin from the castor bean and Shiga toxin from *Shigella* bacteria). Other biological toxins, most notably Staphylococcal toxins A and B, botulinum toxins, and a variety of fungal mycotoxins, can be mass-produced by rogue nations for biological warfare and agricultural and antipersonnel terrorism. Many biological toxins, such as poison hemlock, pyrethrin, and red squill, and man-made toxoids, such as arsenic and thallium salts and pyrethroids, have long been used as pesticides, fungicides, and even as human poisons. Several types of poison gases, including both vesicant and neurotoxic agents, were intentionally released during World War I and in very recent wars (Iran-Iraq War) and terror attacks (Sarin nerve gas attacks in Japan).

This book will serve as a visual and written reminder of the ubiquitous sources of toxins and toxoids in the environment and the outcomes of accidental or intentional toxic exposures in humans. This book will not serve as a comprehensive, major reference source for all toxicologic emergencies; many such comprehensive and even subspecialized toxicology texts are now available. The key features and benefits of this book include serving as a handy atlas and review outline of human poisoning with photographs and diagrams of toxic plants and animals, their mechanisms of poisoning or envenoming, and the human lesions (anatomic, electrocardiographic, and radiographic) caused by toxic exposures. In addition, this text combines the four subspecialties of toxicology (Analytical, Medical, Environmental, and Industrial) into one comprehensive atlas with bulleted text, tables, and figure legends that treat toxic exposures in both children and adults. This book will be a useful study guide for emergency physicians, military physicians, pediatricians, public health physicians and veterinarians, and health science and medical students and graduates in training or practice, or preparing to take image-intense specialty or subspecialty board examinations. Finally, this text will serve as a ready reference for current health science students who seek immediate visual association of venomous species and toxicokinetics with the rapid identification of envenoming species, the clinical and diagnostic outcomes of envenoming or poisoning, and the recommended treatment strategies to limit toxic exposures and injuries.

This text is intentionally organized in a clinical encounter fashion, beginning with a discussion of general poisoning management and useful antidotes and later detailing specific management strategies and antidotes for separate poisonings and envenomings. The book concludes with chapters on biochemical warfare agent exposure and research design and analysis. Biological and chemical terrorism and warfare agents are timely subjects that are still evolving, particularly in the areas of early detection by biosurveillance monitoring systems and real-time polymerase chain reaction (PCR) analyses and personnel protection by preventive immunization, rapid decontamination, specific reversal agents, and personal protective equipment.

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The author also recognizes and appreciates the cooperation and support of the Audubon Nature Institute and its dedicated staff of biologists and naturalists in New Orleans, Louisiana. Audubon Institute staff photographed many of the venomous arthropods, amphibians, and reptiles featured in this book with delicate care and close attention to natural habitats and settings. In particular, the author recognizes the following professional biologists, who provided valuable consultation to the author and contributed their personal photographs to the atlas: (1) Dino Ferri, Assistant Curator of Amphibians and Reptiles; and (2) Zack Lemann, Curator of Arthropods, both of the Audubon Nature Institute in New Orleans, Louisiana.

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About the Author

A native of New Orleans, Louisiana, Dr. James H. Diaz earned several degrees with distinction from Tulane University, including Bachelor of Science, Doctor of Medicine, Master of Health Administration, Master of Public Health and Tropical Medicine, Diploma in Clinical Tropical Medicine and Travel Health, and Doctor of Public Health. Dr. Diaz is board-certified in anesthesiology, critical care medicine, pain management, general preventive medicine and public health, occupational and environmental medicine, and medical toxicology. He currently serves as Professor of Public Health and Program Head, Environmental and Occupational Health Sciences, at the Louisiana State University (LSU) Schools of Medicine and Public Health in New Orleans, Louisiana, and as Adjunct Professor of Pathobiological Sciences at the LSU School of Veterinary Medicine in Baton Rouge, Louisiana.

Dr. Diaz has published more than 100 original articles and chapters in scientific journals and textbooks and is the editor and primary contributing author of *Perinatal Anesthesia and Critical Care*, W.B. Saunders, Company, 1991. Dr. Diaz's current clinical interests include the practices of general preventive medicine and public health, occupational medicine, environmental and travel medicine, and medical toxicology. His current academic interests include: (1) occupational and environmental cancer and injury risk factors; (2) environmental and tropical diseases of travelers; (3) emerging environmentally associated infectious diseases, particularly food-borne, waterborne and vector-borne communicable diseases; (4) human envenomings; and (5) poisonings with natural, alternative, and over-the-counter pharmaceuticals. In 2001, Dr. Diaz was elected to lifetime membership in Delta Omega, the national public health honor society, for academic scholarship and contributions to population health promotion, disease and injury prevention, and preventive medical practice.

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The Pharmacology of Human Poisonings

Chapter Outline

Definitions

Absorption

- Routes of absorption
- Routes vs. rates of absorption
- Rates vs. bioavailabilities
- Toxin transport mechanisms

Distribution

- Bound vs. unbound drugs
- Physiochemical determinants of xenobiotic distribution
- Bioavailability, concentration, and the volume of distribution (V_d)
- Classical compartment models of distribution

Metabolism

- Metabolic reactions
- Drug interactions
- Pharmacogenetics
- Pharmaceutical excipients
- Therapeutic Index (TI)
- Dose-response relationships

Excretion

- Drug elimination kinetics
- Plasma clearance of xenobiotics
- Renal elimination of xenobiotics
- Enhanced *in vivo* elimination of xenobiotics
- Enhanced extracorporeal elimination of xenobiotics

Poisoning in the elderly

- Behavioral and physical considerations
- Pharmacokinetic considerations

Poisoning in children

- Epidemiology
- Ingested agents
- Most commonly ingested agents
- General management

Definitions

Xenobiotics: Foreign, natural, or man-made (synthetic) chemicals, including drugs, pesticides, environmental, and industrial agents.

Pharmacokinetics: The application of mathematical models to describe and predict the behavior of drugs during their absorption, distribution, metabolism, and elimination.

Pharmacodynamics: The relationships of drug concentrations to their observed clinical effects.

Toxicokinetics: The application of mathematical models to describe and predict the behavior of xenobiotics in toxic or excessive doses during their absorption, distribution, metabolism, and excretion.

Toxicodynamics: The relationships of toxic concentrations of xenobiotics to their observed clinical effects.

Absorption

Routes of Absorption

Enteral Administration

Oral: Variable absorption, yet most commonly used route; subjects all xenobiotics to first-pass hepatic metabolism; oral doses often diluted by foods; intestinal absorption delayed by enteric coatings, drug concretions and bezoars, anticholinergics, sedatives, and drug-induced pylorospasm.

Sublingual: Xenobiotics enter systemic circulation closer to the central nervous system (CNS) without first pass, avoiding gastric delays and inactivation. Example: nitroglycerin (NTG).

Rectal: Also avoids gastric delays and inactivation; useful during nausea and vomiting; provides shortcut to central circulation and reduces first pass by 50%.

Parenteral Administration

Intravascular: Intravenous route (iv) most commonly used; avoids both gastrointestinal tract and first-pass hepatic metabolism; useful for drugs poorly absorbed by or unstable in gastrointestinal tract. Example: insulin, lidocaine.

Intramuscular and subcutaneous: Good for slow, sustained delivery of depot preparations of drugs. Example: antibiotics.

Intrathecal and intraventricular: Used primarily for cancer drugs, local anesthetics, opioids, and antibiotics. Caution: use only sterile, preservative-free medications to avoid risks of chemical arachnoiditis. Example: preservative-free morphine and clonidine for chronic pain.

Delayed Gastrointestinal Absorption

Delayed gastric emptying: Often results from fatty meals, anticholinergics, antiserotoninergics (ondansetron), barbiturates, ethanol, glutethimide, methaqualone, and opioids.

Drug coatings, bezoars (undigested food or foreign [hair] proteinaceous materials), concretions: Will all require initial disintegration prior to

absorption. Example: enteric-coated tablets, long-acting preparations, meprobamate (frequently forms concretions), foods (persimmons = form phytobezoars).

Gastric outlet pylorospasm: Most frequently caused by common gastric irritants. Example: iron, salicylates.

Routes vs. Rates of Absorption

Routes of Absorption

Enteral: Oral, rectal.

Parenteral: Intradermal, subcutaneous, intravascular (intravenous, intra-arterial), intramuscular.

Cutaneous: Topical and transdermal.

Miscellaneous: Inhalation, sublingual, transmucosal, intranasal, intrathecal, intraventricular.

Rates of Absorption

Fastest-to-slowest: Intravascular > inhalation > sublingual > intranasal > intramuscular > rectal > oral > subcutaneous > topical > transdermal.

Rate of absorption: Predicts the onset of action of xenobiotics.

Extent of absorption: Predicts the bioavailability of the xenobiotic or the extent of its pharmacologic effect. Example: digoxin has 50% bioavailability.

Rates vs. Bioavailabilities

Physiochemical Factors Influencing Absorption

Physical Factors

Molecular weight (MW): Low MW promotes rapid absorption by passive diffusion.

Blood flow: High blood flow favors high absorption. Example: intestinal > gastric absorption.

Surface area: High surface area favors high absorption. Example: intestinal > gastric absorption.

Contact time: Absorption is inversely proportional to gastrointestinal transit time. Example: cathartics speed transit time and limit absorption.

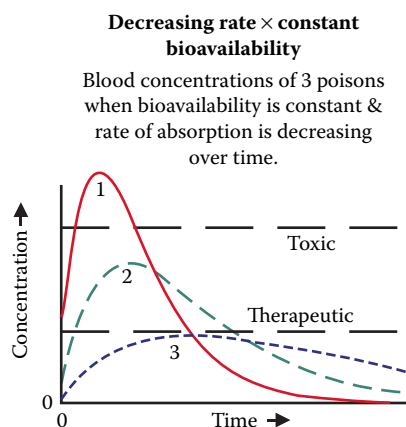


FIGURE 1.1a The blood concentrations of three poisons when bioavailability is constant and rate of absorption is decreasing over time.

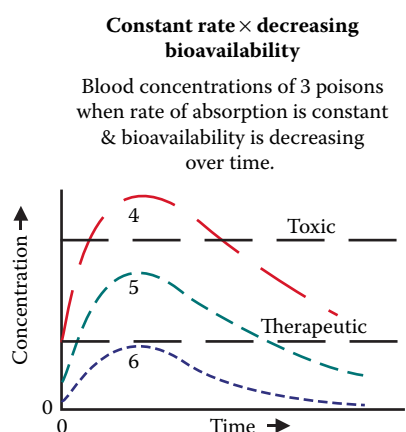


FIGURE 1.1b Constant rate \times decreasing bioavailability. The blood concentrations of three poisons when rate of absorption is constant and bioavailability is decreasing over time.

Chelators of heavy metal toxins enhance the bioavailability of safer, complexed toxins, but have no impact on transit time or absorption, unless combined with cathartics. Example: deferoxamine and Fe, penicillamine and Cu, succimer and Pb.

Solubility, Polarity, pH

Water solubility: Water-soluble (hydrophilic) xenobiotics cannot cross lipoprotein membranes and must filter through aqueous channels.

Lipid solubility: Lipid-soluble (lipophilic) xenobiotics readily cross lipoprotein membranes for increased absorption and often enter enterohepatic cycles that decrease renal elimination. Example: Opioids: Fentanyl. From long-acting

to short-acting; Carfentanil > fentanyl > sufentanil > alfentanil.

Polarity: Lack of polarity or charge favors enhanced absorption by passive diffusion.

pH: Acidic drugs (ASA) demonstrate increased absorption in the acidic stomach; basic drugs demonstrate increased absorption in the alkaline intestine (jejunum > ileum).

Toxin Transport Mechanisms

Passive Diffusion

Concentration gradient: The gradient between high-to-low concentrations that provides the driving force for passive diffusion.

Saturation potential: None; passive diffusion is not susceptible to saturation or zero-order kinetics.

Energy source: Concentration gradients alone.

Fick's Law of Diffusion: Governs the rate of passive diffusion = $dQ/dT = DAK (C_1 - C_2)/h$, where D = diffusion constant, A = surface area of membrane, and $C_1 - C_2$ = difference in poison concentrations on either side of membrane.

Active Transport

Carrier protein: Required for active transport against concentration gradients.

Saturation potential: High; protein carriers are often saturated in overdose, allowing toxins to accumulate in the central circulatory compartment.

Energy source: Energy is provided by the hydrolysis of ATP. Active transport is a highly energy-dependent process.

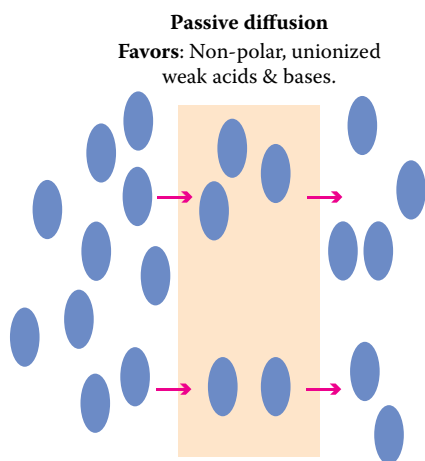


FIGURE 1.2a Passive diffusion favors nonpolar, unionized weak acids and bases.

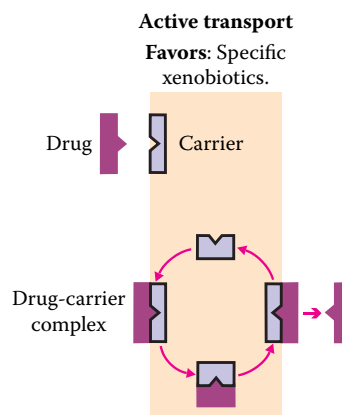


FIGURE 1.2b Active transport favors specific xenobiotics.

Distribution

Bound vs. Unbound Drugs

Bound Drugs

- Specialized proteins bind xenobiotics in plasma and tissue compartments, making toxins unavailable for distribution.
- **Albumin:** Binds acidic (“A”) drugs with low V_d = aspirin, phenoxyacetic acid herbicides, anticonvulsants, anticoagulants (warfarin or coumadin).
- **α -1-acid glycoprotein:** Binds basic (“B”) drugs with low V_d = β -blockers, amide local anesthetics, tricyclic antidepressants (TCAs).
- **Specialized carrier proteins:** Exist in the blood—transferrin (carries Fe); in the kidney—metallothionein (carries Cd, Pb, and Hg); and in the retina—melanin (carries chloroquine and chlorpromazine [CPZ]).

Unbound Drugs

- Only unbound drugs freely distribute through membranes to tissues.
- **Bioavailability:** Applies to unbound drugs only.
- **Saturation or zero-order kinetics:** Toxic overdoses often saturate protein binders and carriers (albumin-binder, transferrin-Fe carrier), making large concentrations of unbound drugs available for tissue distribution and organ toxicity. Example: ASA-CNS toxicity; Fe-hepatotoxic and cardiotoxic.
- **Lab serum concentrations:** Of limited value in determining serum concentrations of unbound drugs because labs measure both bound and unbound drugs to determine serum values that closely approximate plasma concentration.

Physiochemical Determinants of Xenobiotic Distribution

- **Blood flow:** Determined by the cardiac output and accounts for initial distribution of xeno-

biotics and preferentially perfuses brain, liver, kidneys > muscle > fat > bone.

- **Drug structure:** Uncharged, hydrophobic, and lipophilic drugs readily cross lipoprotein membranes.
- **Protein binding:** Plasma and specialized carrier proteins sequester xenobiotics in the central plasma compartment and often become saturated, resulting in high plasma concentrations of unbound toxins.
- **Physiologic barriers:** Protect downstream target organs from xenobiotic distribution and toxicity. Example: blood–brain barrier, placental barrier, blood–testis barrier.

Bioavailability, Concentration, and the Volume of Distribution (V_d)

Definitions and Relationships

- V_d : The theoretical volume into which a drug distributes.
- V_d : Determines how much of a drug remains inside or outside the central circulatory (plasma) compartment sampled by serum concentrations.
- V_d : Drugs with $V_d < 1$ L/kg remain inside the plasma compartment available for removal by hemodialysis (HD). Example: ASA $V_d = 0.2$; ethylene glycol (antifreeze) $V_d = 0.6$.
- V_d : Drugs with $V_d > 1$ L/kg distribute from plasma to tissues and are unavailable for removal by HD. Example: digoxin $V_d = 5$; TCA $V_d = 10$ – 15 .

Determinants of the V_d

- Drug dose administered
- Drug bioavailability
- Peak plasma concentration
- Formula: $V_d = \text{dose in mg/kg} \times \text{bioavailability (\%)} / \text{plasma concentration}$. Alternatively, $\text{plasma concentration} = \text{dose in mg/kg} / V_d \times \text{weight in kg}$

Classical Compartment Models of Distribution

One-Compartment Model

- **Definition:** Some xenobiotics rapidly enter the central circulatory compartment for rapid distribution to tissues; plasma concentrations mirror tissue concentrations.

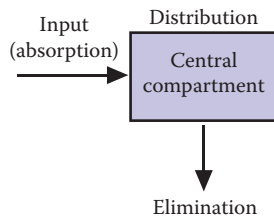


FIGURE 1.3a One-compartment distribution model. Some xenobiotics rapidly enter the central circulatory compartment for rapid distribution to tissues; plasma concentrations mirror tissue concentrations.

Two-Compartment Model

- **Definition:** Most xenobiotics do not instantaneously equilibrate with tissues, but are initially distributed to highly perfused organs, and subsequently distributed to less perfused peripheral tissues. Example: Digoxin, barbiturates, lidocaine.

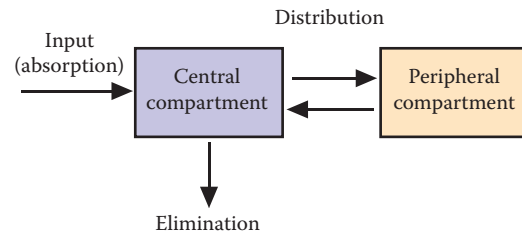


FIGURE 1.3b Two-compartment distribution model. Most xenobiotics do not instantaneously equilibrate with tissues, but are initially distributed to highly perfused organs, and subsequently distributed to less perfused peripheral tissues. Ex: barbiturates, digoxin, lidocaine.

Metabolism

Metabolic Reactions

Phase I Hepatic Reactions

- **Mechanisms:** Preparative or nonsynthetic reactions that often precede phase II reactions and either add oxygen and introduce polar groups to (by oxidation > reduction and hydrolysis) or expose polar groups on (by dealkylation) xenobiotics to increase their polarity and water solubility in preparation for further hepatic metabolism (by phase II) or renal elimination.
- **Enzymes:** All phase I enzymes are members of the hepatic microsomal (endoplasmic reticulum fraction) mixed function oxidase (oxygen-adding) enzyme system (Cytochrome [CY] P-450 family). All phase I hepatic reactions require the reducing agent nicotinamide adenine dinucleotide phosphate (NADP) to add O₂ to and increase the polarity of xenobiotics.

Phase II Hepatic Reactions

- **Mechanisms:** Synthetic reactions that often replace or follow, but rarely precede, phase I reactions, designed to conjugate polar groups, reduce electric charges, and assure water solubility for the ultimate renal elimination of xenobiotics. Conjugation occurs with glucuronide > sulfate, acetate, methyl groups, or amino acids (glycine > taurine and glutamic acid).
- **Enzymes:** Phase II hepatic enzymes may belong to either the liver's microsomal (CYP-450) or cytosolic fractions.

Common Members of the CYP-450 Hepatic Enzyme Family and Their Representative Enzyme Substrates

- CYP1A1 — Polycyclic aromatic hydrocarbons (PAHs)
- CYP1A2 — Acetaminophen
- CYP2A6 — Nicotine
- CYP2D6 — Debrisoquine
- CYP2F1 — Ethanol

- CYP3A4 — Many antiarrhythmics, oral contraceptive pills (OCPs), warfarin. The most important member of the CYP-450 family that metabolizes many drugs, including macrolide antibiotics (erythromycins), antifungal azoles, the nonsedating antihistamines (astemizole and terfenadine – Seldane®), and cisapride (Propulsid®). When two or more drugs metabolized by CYP-450 3A4 are prescribed, the toxicity of the slowest metabolized drug can be enhanced, producing adverse effects. Both terfenadine and cisapride caused QRS widening and, rarely, fatal torsades de pointes when prescribed with other 3A4-metabolized drugs and were withdrawn from the market by the U.S. Food and Drug Administration (FDA).

Drug Interactions

Hepatic Enzyme Inducers

- Increase substrate drug metabolism and thereby decrease therapeutic drug efficacy.
- **Anticonvulsants:** Barbiturates, carbamazepine, phenytoin, primidone.
- **Sedatives:** Ethanol, glutethimide.
- **Antibiotics:** Isoniazid (INH), rifampin (decreases efficacy of oral contraceptive pills [OCPs]), griseofulvin.
- **Miscellaneous:** Omeprazole, polycyclic aromatic hydrocarbons (PAHs), St. John's wort (can decrease efficacy of cycloserine, indinavir, and oral contraceptives (OCPs); interacts with selective serotonin reuptake inhibitors (SSRIs), and has been associated with suicides and deaths in depressed patients on SSRIs, possibly associated with central serotonin excess).

Hepatic Enzyme Inhibitors

- Decrease substrate drug metabolism, usually increasing toxicity of drug, but decreasing toxicity of metabolites. Example: cimetidine for mushroom poisoning to block the metabolism of the hepatotoxic poison, amanitin.

- **Antifungals:** All azoles.
- **Antibiotics:** All macrolides, chloramphenicol, primaquine, trimethoprim-sulfamethoxazole, ciprofloxacin.
- **Antiarrhythmics:** Amiodarone, β -blockers, quinidine, verapamil.
- **H₂-blockers and proton-pump inhibitors:** Cimetidine, ranitidine, omeprazole.
- Most antipsychotics and tricyclic antidepressants (TCAs).
- **Miscellaneous:** Allopurinol, OCPs, grapefruit juice.

Pharmacogenetics

Genetic Polymorphisms

- **Definition:** Inherited (autosomal recessive, often X-linked), inter-individual differences in the structure and function of specific hepatic microsomal or cytosolic enzymes that alter either phase I or phase II hepatic metabolic reactions to promote or, more rarely, to reduce the toxicity of xenobiotics, usually therapeutically administered drugs. Example: fast (decreased efficacy) vs. slow (increased toxicity) acetylators of the anti-tuberculosis drug isoniazid (INH).

Common Genetic Polymorphisms

- **Fast vs. slow INH acetylators:** 95% of Asians and Blacks are fast (rapid) acetylators of INH at lower risk of INH neurotoxicity; 50% of Americans and >70% of Scandinavians are slow acetylators at higher risk of INH toxicity.
- **Pseudocholinesterase deficiency:** 2% of Americans and most Alaskan and Canadian Inuits cannot metabolize ester local anesthetics (including cocaine) and succinylcholine with higher risks of toxicity, especially cocaine-induced myocardial infarction (MI) and CVA, and succinylcholine-prolonged paralysis.
- **Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency:** Common in Blacks (confers malaria protection) and renders red blood cells incapable of responding to oxidative structural stresses imposed by oxidant drugs (nitrites, sulfa), resulting in hemolysis or methemoglobinemia, often refractory to methylene blue reversal.

Pharmaceutical Excipients

What Are Excipients?

- **Definition:** Excipients are the chemical ingredients other than active drugs that are included in pharmaceutical preparations for a variety of reasons.
- **Uses:** Binders, coatings, colors, diluents, disintegrators, flavorings, preservatives, sweeteners, solvents.

Commonly Used Excipients

Colors: Dyes can cause allergic reactions. Example: FD&C Reds 40 and 19, carmine, quinolone yellow.

Flavorings: Licorice (glycyrrhizic acid) inhibits cortisol metabolism, causing or exacerbating hypertension and promoting hypokalemia.

Sweeteners: Aspartame is contraindicated in phenylketonurics.

Preservatives: Benzyl alcohol in IV flush solutions and multi-dose medication vials can cause acidosis and shock in preemies – “Gasping Baby” Syndrome.

Solvents: Polyethylene glycol in IV drugs irritates veins and has caused metabolic acidosis and acute renal failure after applying topical antimicrobial (sulfonamides) creams for extensive burn therapy.

Therapeutic Index (TI)

What Is the Therapeutic Index (TI)?

- **Definition:** The TI is the ratio of the dose of a drug that causes toxicity to the dose that produces the desired and intended effect. The TI can only be determined by administering increasing drug doses to volunteers and observing for toxic responses.

How Is Drug Safety Assessed? (by large vs. small TIs)

- **Large TI = a large therapeutic window:** Large doses of the drug are relatively safe to administer, unless drug allergy exists. Close patient monitoring is unnecessary due to drug's safety profile. Example: penicillin, OCPs.
- **Small TI = a small therapeutic window:** Drug toxicity is possible even at low drug doses. Drug

serum concentrations and early toxic effects must be closely monitored. Example: warfarin-monitor the INR or PTT, digoxin-monitor dig levels, serum K.

Dose-Response Relationships

Receptor Theory

- **Definition:** Many xenobiotics bind to specific protein receptors by ionic forces > hydrophobic or hydrophilic forces > Van der Waals forces to create a stable drug-receptor complex, the key to traversing lipoprotein membrane barriers and entering organ and tissue compartments.

Receptor States

Agonist: Xenobiotic that activates protein receptor and opens barriers to tissues.

Partial agonist: Xenobiotic that only partially activates protein receptor.

Antagonist: Xenobiotic that totally prevents the binding of an agonist to its specific protein receptor.

Partial antagonist: Xenobiotic that partially prevents the binding of an agonist to its specific protein receptor.

Mixed agonist/antagonist: Xenobiotic that both activates some receptors and paradoxically inhibits

other receptors. Example: Butorphanol, nalbuphine, pentazocine.

Competitive antagonist: Xenobiotic that competes with agonist for its receptor.

Noncompetitive antagonist: Xenobiotic that interferes with agonist binding.

Efficacy vs. Potency (ED_{50})

How Effective Is the Drug?

- **Definition:** Efficacy is a measure of the maximal effective response produced by a drug. Efficacy depends on the number of drug-receptor complexes formed and the efficiency with which the activated complex produces a cellular response.

How Potent Is the Drug?

- **Definition:** Potency is a measure of how much of a drug is required to elicit a given response.
- Potency is expressed as the **effective dose 50** [ED_{50}] or the dose of a drug that elicits 50% of the maximal response.
- The lower the dose required for a given response, the more potent the drug.
- Potent drugs have steep dose-response curves (plasma concentration vs. time) demonstrating that small increases in drug dose will elicit large changes in response. Example: digoxin, warfarin.

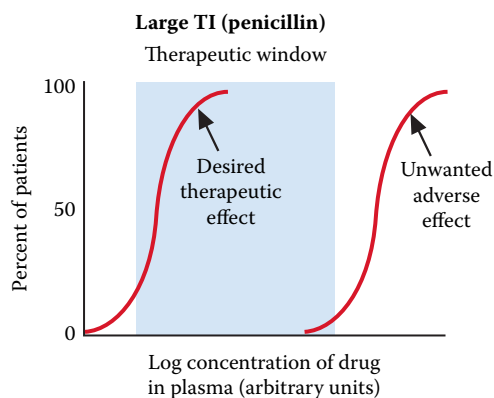


FIGURE 1.4a Large therapeutic index. A large therapeutic index reflects a large therapeutic window in which large doses of a drug are relatively safe to administer, unless drug allergy exists. Ex.: penicillin.

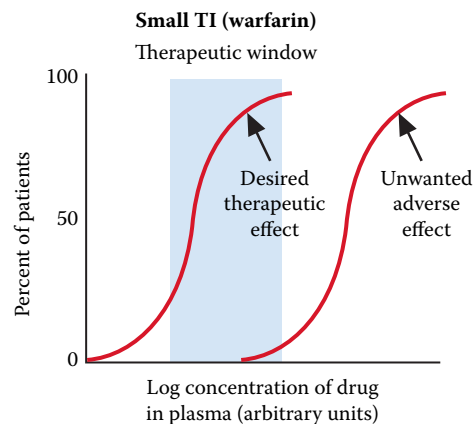


FIGURE 1.4b Small therapeutic Index. A small therapeutic index reflects a small therapeutic window in which drug toxicity is possible even at low doses. Ex.: digoxin, warfarin.

Excretion

Drug Elimination Kinetics

First-Order Kinetics

- The rate of a drug's elimination is directly proportional to its plasma concentration. The higher the concentration, the more rapid the drug elimination. Drug decay curve is curvilinear. Example: 90% of all drugs.

Zero-Order Kinetics

The rate of a drug's elimination is independent of its concentration because (1) the drug's hepatic metabolizing enzyme system quickly becomes saturated to capacity, and (2) a constant, predictable amount of drug is eliminated per unit of time. Drug decay curve is linear. Example: ethanol.

Combined Elimination or Michaelis-Menten Kinetics

The rate of a drug's elimination is initially first order, and then switches to zero order when the drug's hepatic metabolizing enzyme system becomes saturated to capacity. Combined elimination kinetics is also known as **Michaelis-Menten** kinetics. Drug decay curve is initially curvilinear and then becomes linear.

Plasma Clearance of Xenobiotics

Definition: Clearance (Cl) is measured as the volume of plasma cleared of a xenobiotic per unit of time.

$$\begin{aligned}\text{Cl} &= \frac{\text{Rate of elimination}}{\text{Plasma concentration}} \times \text{Time} \\ &= \text{Rate of elimination} \times V_d \\ &= \text{IV dose administered} / \text{Area Under the Curve (AUC) of } C \times t\end{aligned}$$

Where C = concentration and t = time.

Renal Elimination of Xenobiotics

1. **Glomerular filtration (GF):** Physical filtering that depends on cardiac output and renal perfusion, and is independent of a drug's pH or lipid solubility; measured as the glomerular filtration rate (GFR), normally 20% of renal plasma flow (600 mL/minute) or 125 mL/minute.
2. **Proximal tubular secretion:** Xenobiotics that are not eliminated from the blood in the glomerular filtrate can be removed later by active transport using specific carrier proteins within the proximal tubules.
3. **Distal tubular reabsorption:** As high concentrations of uncharged, water-soluble (hydrophilic) phase I drug metabolites reach the distal convoluted tubules (DCTs), concentration gradients are created between the DCTs and the central circulatory compartment, allowing drug metabolites to be reabsorbed into plasma. Conversely, phase II hepatically metabolized drugs remain highly ionized, become trapped in the urine, and are unable to back-diffuse into the central circulation. Example: alkalinization of the urine with sodium bicarbonate and forced diuresis with IV fluids will ion-trap acidic ASA and phenoxyacetic acid herbicide metabolites in the urine and augment GFR for enhanced elimination of toxic metabolites.

Enhanced *In Vivo* Elimination of Xenobiotics

Corporeal Enhanced Elimination

Alkaline diuresis: Traps weak acids and their metabolites (barbiturates, phenoxyacetic acid herbicides, salicylates-ASA) in the DCTs and enhances their renal excretion.

Gut dialysis: Multiple doses of oral activated charcoal (AC) use reverse diffusion gradients to back diffuse xenobiotics with low V_d values (<1 L/kg) from the plasma compartment and back into the gut for fecal excretion. Example: multiple doses of AC are often indicated for theophylline poisoning.

Extracorporeal Enhanced Elimination

Hemodialysis (HD): Most effective means of extracorporeal elimination of xenobiotics.

Hemoperfusion (HP): Only effective for drugs that are adsorbed to AC. Example: theophylline.

Hemofiltration (HF): Effective for the slow and prolonged removal of high-molecular-weight (4,500–40,000 Daltons) compounds, not amenable to hemodialysis (<500 Daltons).

Peritoneal dialysis: Ineffective for the enhanced elimination of xenobiotics and not recommended for poisonings.

Enhanced Extracorporeal Elimination of Xenobiotics

Extracorporeal Enhanced Elimination

Indications for Enhanced Elimination

- Poisoned patients not responding to supportive care.
- Poisoned patients with impaired hepatic or renal elimination systems.
- Severely poisoned patients with high drug concentrations associated with high morbidity and mortality. Example: ethylene glycol.
- Poisoned patients at high risks due to advanced age, pregnancy, or concurrent diseases.
- Poisoned patients with co-existing and non-responsive volume or electrolyte disturbances. Example: fluid overload, acidosis, hyperkalemia.

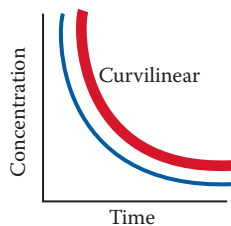


FIGURE 1.5a First-order kinetics. The rate of a drug's elimination is directly proportional to its plasma concentration. Thus, the higher the drug concentration, the more rapid is the drug's elimination. Ex.: most drugs.

Drug Factors Favoring the Use of Enhanced Elimination

- Low $V_d < 1$ L/kg; Example: ASA, ethylene glycol
- Low molecular weight (MW): <500 Daltons
- Water-soluble compounds
- Non-protein-bound compounds
- Low endogenous renal clearance
- One-compartment model kinetics

Enhanced Elimination Techniques

Hemodialysis: Success requires that the toxin be of low MW and low V_d , water soluble, and not protein bound. Complications include bleeding, thrombosed access sites, and the elimination of therapeutic drugs, antidotes (folic acid), and water-soluble vitamins (vitamin K). Example: bromides, ethanol, methanol, ethylene glycol, chloral hydrate, lithium, and ASA are easily dialyzed.

Hemoperfusion: Success requires that the toxin be adsorbed to AC. Preferred for poisoning with theophylline and anticonvulsants (carbamazepine, phenobarbital, and phenytoin).

Hemofiltration: Not as effective as HD or HF, but can be continued for days with fewer complications. Advantages include ability to eliminate high MW (4500–40,000 Daltons) and protein-bound toxins. Preferred for toxins slowly eliminated from tissue binding sites. Example: aminoglycosides, lithium, and procainamide.

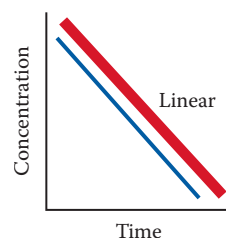


FIGURE 1.5b Zero-order kinetics. The rate of the drug's elimination is independent of its concentration, and a constant amount of drug is eliminated per unit time. Ex.: ethanol.

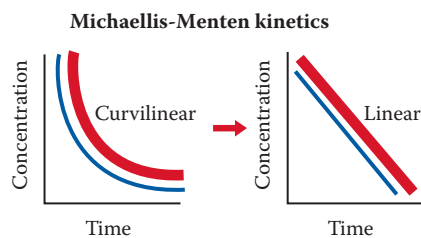
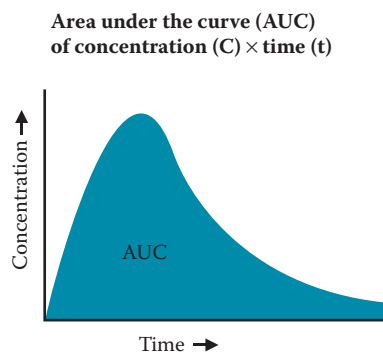


FIGURE 1.6 Michaelis-Menten Kinetics. The rate of a drug's elimination is initially by first-order kinetics, and then switches to zero-order kinetics when the drug's hepatic metabolizing enzyme system becomes saturated to capacity.

FIGURE 1.7 Plasma clearance. Plasma clearance is reflected by the area under the curve of a drug's plasma concentration over time, or clearance = the rate of elimination/plasma concentration \times time.



Poisoning in the Elderly

Behavioral and Physical Considerations

- **Reduced muscle mass and increased body fat:** Promotes increased Vd of lipophilic toxins.
- **High total body water:** Promotes increased Vd of water-soluble toxins.
- Compliance problems.
- **Age-related CNS problems:** Confusion, depression, disorientation, dementia.
- **Dosing problems:** Multiple medications, drug tolerance.

Pharmacokinetic Considerations

- **Absorption:** Decreased gastric acid secretion and decreased gut motility may increase drug toxicity.
- **Distribution:** Decreased albumin binding and increased α 1-acid glycoprotein binding, coupled with decreased gut and hepatic perfusion, may increase drug toxicity.
- **Metabolism:** Decreased phase I hepatic metabolism; phase II hepatic metabolism remains unchanged.
- **Excretion:** Decreased renal plasma flow (RPF) = decreased glomerular filtration rate (GFR) = decreased excretion by filtration.

Poisoning in Children

Epidemiology

- 67% of annual poisonings occur in children ≤19 years old. Ingestion is the route of exposure in 76% of cases.
- Children <5 years old have the highest rate of poisoning visits to emergency departments.

Ingested Agents

- Most commonly ingested agents include cosmetics and personal care products.
- 52% are medications.
- 48% are non-medications.
- Most lethal agents: cocaine, anticonvulsants, antidepressants, cleaning products, hydrocarbons.

Most Commonly Ingested Agents

Cosmetics and personal care products
Cleaning products
Analgesics
Plants
Cough and cold preparations
Foreign bodies
Topical agents
Pesticides
Vitamins
Hydrocarbons

General Management

Ipecac: Use at home within 1 hour of ingestion if directed. Avoid with coma, convulsions, corrosives, hydrocarbons, coagulants, and in children under the age of 6 years.

Position: Left lateral decubitus, Trendelenburg (left side down, head down).

Lavage: Only with airway protection and life-threatening (TCA) overdose within 1 hour.

AC: Administer 1g/kg within first hour; ineffective for alcohols, corrosives, hydrocarbons, metals, and minerals.

MDAC: Consider for carbamazepine, phenobarbital, theophylline.

Cathartics (indicated with MDAC): Mg citrate > sorbitol, whole-bowel irrigation for slow-release drugs, iron and lithium, body packers and stuffers (cocaine and heroin).

The General Management of the Poisoned Patient

Chapter Outline

Preventing gastrointestinal absorption of the toxin

- Gastric emptying
- Emesis vs. lavage
- Activated charcoal (AC) and multi-dose activated charcoal (MDAC)
- Cathartics
- Whole-bowel irrigation (WBI)
- Alternative methods of gastrointestinal emptying

Enhancing elimination of the toxin

- Methods

Preventing Gastrointestinal Absorption of the Toxin

Gastric Emptying

Indications for Gastric Emptying

- High-risk, potentially lethal ingestions: Aspirin, calcium channel blockers (CCBs) (especially verapamil), chloroquine, colchicine, cyanide, tricyclic antidepressants (TCAs).
- Recent ingestions, less than 1 to 2 hours, especially for slow-release drugs.
- Consequential toxicity: Seizures, hypotension, arrhythmias.
- Ineffective or nonexistent antidotes: CCBs, iron, colchicine, paraquat, selenious acid.
- Enteric-coated or slow, sustained-release tablets: Aspirin, theophylline, verapamil.
- Poisonings with agents that reduce gastrointestinal motility: Anticholinergics, opioids, sedative/hypnotics.
- Poisonings with agents that cause pylorospasm and gastric outlet obstruction: Aspirin, meprobamate, iron.
- Poisonings with agents that form gastric concretions or masses: Aspirin, enteric-coated and sustained-release tablets, iron, meprobamate, phenobarbital.

Contraindications to Gastric Emptying

- Caustic acid/alkali ingestions
- Hydrocarbon ingestions
- Sharp and pointed material ingestions
- Drug packet ingestions
- Bleeding diathesis, coagulopathies
- Esophageal varices and Mallory-Weiss tears of the esophagus
- Significant vomiting
- Nontoxic ingestions



FIGURE 2.1 Non-dissolving radiopacities in the gastrointestinal tract. Abdominal radiograph of a 3-year-old boy with a history of ingesting leaded paint chips peeling off doors and windows. Note radiopaque leaded paint chips in colon and rectum. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Ipecac Emesis

Indications

- Witnessed ingestions, usually at home
- Home use; contraindicated in the emergency department (ED)
- Ingestions of objects too large for lavage tubes
- Ingestions by infants older than 6 months and small children



FIGURE 2.2 Body stuffer: heroin. Axial abdominal oral and intravenous contrast-enhanced computerized tomogram (CT) at the level of the renal veins that demonstrated a rectangular container of heroin in a jejunal loop. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Contraindications

- Potential or compromised airway protective reflexes
- Imminent seizure or coma: Isoniazid, camphor, meperidine
- Imminent deterioration: tricyclic antidepressants, meperidinepropoxyphene, propranolol, tramadol
- Caustic acid/alkali ingestions
- Hydrocarbon ingestions
- Sharp material ingestions
- Increased risks of bleeding
- Significant vomiting
- Nontoxic ingestions

Dose

- Adults and children older than 5 years old: 30 mL (2 Tbsp.); may repeat one time
- Children 1 to 5 years: 15 mL (1 Tbsp.)
- Infants 6 to 12 months: 10 mL (2 tsp.)

Complications

- Intractable vomiting (rare), delayed emesis while unconscious

- Mallory-Weiss esophageal tears
- Pneumomediastinum
- Aspiration pneumonitis
- Delaying activated charcoal administration
- Electrolyte abnormalities
- Substance abuse = bulimia

Emesis vs. Lavage

Orogastric Lavage

Indications

- High-risk ingestions when a drug or toxin is still accessible in the stomach (<1 hour)
- Ingestions that delay gastric emptying, cause gastric outlet obstruction, or form gastric concretions
- Ingestions of enteric-coated or sustained-release preparations

Contraindications

- Compromised or unprotected airway
- Caustic acid or alkali ingestions
- Sharp material ingestions
- Drug packet ingestions
- Bleeding diathesis or increased risks of gastrointestinal hemorrhage
- Prior significant emesis
- Nontoxic ingestions

Procedure

- Adults: 36–40 French orogastric tube
- Children: 22–28 French orogastric tube
- Endotracheal tube if airway is compromised
- Left lateral decubitus position
- Confirm proper orogastric tube placement by x-ray
- Lavage in aliquots: Adults 250 mL/kg and children 10 mL/kg of normal saline until clear; maximum 1 L for children.
- Instill activated charcoal (AC) via orogastric tube



FIGURE 2.3 Orogastric tube-induced gastric perforation with pneumomediastinum. Computerized axial tomogram (CT) of the chest that demonstrates a huge pneumomediastinum surrounding the distal esophagus, heart, and descending thoracic aorta following the insertion of an orogastric tube for gastric lavage and activated charcoal (AC) administration. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Complications

- Inadvertent tracheal intubation or airway trauma
- Esophageal/gastric perforation with pneumomediastinum, mediastinitis, or hemorrhage
- Emesis
- Aspiration pneumonitis

Activated Charcoal (AC) and Multi-Dose Activated Charcoal (MDAC)

Indications

- **Activated Charcoal (AC):** Any substance known to bind to AC, especially highly toxic substances
- **Multi-Dose Activated Charcoal (MDAC):** All drugs and toxins known to bind with small volumes of distribution (less than 1 L/kg), low renal clearance, little protein binding, and enterohepatic recirculation of toxic metabolites
- Drugs that reduce gastrointestinal motility, form gastric concretions, and enteric-coated or sustained-release preparations

Contraindications

- Patients at risk for aspiration with unprotected airways
- Caustic acid and alkali ingestions
- Ileus or small bowel obstruction
- Most hydrocarbon (need endoscopy) and heavy metal ingestions: Hydrocarbons and metals do not bind to AC
- Most large-volume (dose usually in grams/kilogram) ingestions: Iron, lithium, ethanol
- Single-substance ingestions of iron, lithium, ethanol

Dose/Procedure

- Initial: 1 g/kg for both adults and children; add sorbitol for initial AC dose only
- **MDAC:** 0.5–1.0 g/kg every 1 to 4 hours, with no additional cathartics
- Consider nasogastric tube and antiemetics to control vomiting
- Allow AC to leave stomach before emptying stomach

Complications

- Aspiration
- Emesis
- Obscuring gastrointestinal mucosa and limiting visibility during endoscopy
- Constipation
- Small bowel obstruction

Cathartics

Indications

- To speed gastrointestinal transit of drugs or toxins that remain in the gastrointestinal tract and may continue to be adsorbed to or desorbed from AC
- Combine only with the initial dose of AC or MDAC and do not repeat

Contraindications

- Abdominal trauma

- Intestinal ileus or small bowel obstruction
- Preexisting diarrhea
- Hypovolemia and dehydration
- Renal failure (Mg citrate and Mg sulfate could cause further neurologic and respiratory depression from hypermagnesemia)
- Routine use in children
- Prior cathartic dose

Dose of Cathartics

- Sorbitol 70% is preferred: Adults 1 g/kg and children 0.5 g/kg
- 10% Mg citrate: 4 mL/kg for children and adults, maximum 300 mL
- Mg sulfate: Adults 1 g/kg and children 0.5 g/kg

Complications

- Excessive diarrhea
- Emesis
- Electrolyte abnormalities
- Hypermagnesemia (Mg citrate and Mg sulfate)
- Hypokalemia
- Hyponatremia or hypernatremia (sorbitol)
- Volume depletion and dehydration
- Hypernatremic dehydration (sorbitol)

Whole-Bowel Irrigation (WBI)

Indications

- **Sustained-release drugs:** Theophylline, calcium channel blockers, especially verapamil
- **Enteric-coated drugs:** Aspirin, verapamil
- **Drugs or toxins not adsorbed by AC:** Iron, heavy metals, lithium, potassium
- **Slowly dissolving substances:** Iron tablets, lead paint chips, bezoars, and concretions
- **Crack vials:** body stuffers, cocaine and heroin
- **Drug packets:** Body packers, cocaine and heroin

Contraindications

- Paralytic ileus or small bowel obstruction
- Abdominal trauma
- Rapidly absorbed drugs and toxins: alcohols

- All liquid ingestions
- Hydrocarbon ingestions
- Caustic acid and alkali ingestions
- Parenterally administered drugs

Dose

- Adults: 2 L/hour
- Children: 0.5 L/hour

Complications

- Vomiting, especially with rapid administration
- Bloating
- Decreased efficiency of activated charcoal
- Rectal itching

Alternative Methods of Gastrointestinal emptying

Other Miscellaneous Binding Agents

- Cholestyramine and colestipol: For methotrexate and organochlorine pesticides — lindane (Kwell®) and chlordecone (Kepone®)
- Sodium polystyrene sulfonate (Kayexalate®): For lithium and potassium



FIGURE 2.4 Slowly dissolving substances: enteric-coated phenothiazine tablets in stomach. Axial oral and contrast-enhanced computerized tomogram (CT) at the stomach level that demonstrates two slowly dissolving radiopaque substances (enteric-coated phenothiazine tablets). (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

- Potassium ferricyanoferrate (Prussian blue): For thallium and cesium
- Fuller's earth (diatomaceous earth): For paraquat and diquat

Surgical Emptying

- Rupture of cocaine drug packets
- Mechanical bowel obstruction by cocaine drug packets, vials, or pipes
- Bezoars: Aspirin, bromide, meprobamate

Enhancing Elimination of the Toxin

Methods

Indications

- Poisons with small volumes of distribution: poison remains in the blood compartment
- Poison with low endogenous renal clearance rates: alcohols, beta-blockers, lithium, phenytoin, paraquat, salicylates, theophylline
- Poisons that are not lipid-soluble or highly protein-bound

Urinary Alkalinization

- **Mechanism:** To trap weak acids in renal tubular fluid to prevent tubular absorption and promote urinary excretion.
- **Indications:** Consider urinary alkalinization for all weak acids, such as salicylates, phenobarbital, chlorpropamide; formic acid (methanol), chlorophenoxyacetic acid herbicides; for methotrexate; and to protect the kidneys during myoglobinuria from rhabdomyolysis.
- **Complications:** Volume overload, metabolic alkalosis.
- **Urine acidification** is not recommended.

Forced Diuresis

- **Mechanism:** To produce diuresis by volume expansion with Na-containing solutions, normal saline, or lactated Ringer's solution; often combined with diuretics.
- **Indications:** Not recommended except to protect the kidneys from myoglobinuria during extensive rhabdomyolysis. Exception: forced Cl diuresis with NaCl and mannitol for platinum (cisplatin) overdose.
- **Complications:** Volume overload and electrolyte disturbances.

Peritoneal Dialysis

- **Mechanism:** To enhance the elimination of water-soluble, low-molecular-weight, poorly protein-bound substances with low volumes of distribution.
- **Indications:** Too slow to be useful and not recommended.

Hemodialysis

- **Mechanism:** To enhance the elimination of water-soluble, very low-molecular-weight (less than 500 Daltons), non-protein-bound compounds with low volumes of distribution (less than 1 L/kg) and low endogenous renal clearance rates (less than 4 mL/kg/min).
- **Indications:** Bromide, lithium, potassium, salicylates, all alcohols (ethylene glycol, methanol, isopropanol), and chloral hydrate and its primary metabolite, trichloroethanol.
- **Complications:** Bleeding, access related complications, air embolism, nosocomial infections.

Charcoal Hemoperfusion

- **Mechanism:** To enhance the elimination of compounds adsorbed by AC in an extracorporeal fashion; can be used in series with hemodialysis.
- **Indications:** Anticonvulsants: carbamazepine, phenobarbital, and phenytoin; theophylline; thallium (exception: thallium is the only heavy metal adsorbed to AC). In series with hemodialysis: carbamazepine, theophylline, procainamide, thallium.
- **Complications:** Same as dialysis + charcoal embolization, leukopenia, thrombocytopenia, hypocalcemia.

Continuous Hemofiltration

- **Mechanism:** To enhance the elimination of very high-molecular-weight (10,000 to 40,000 Da) compounds using the patient's own arterial pressure (continuous arteriovenous hemofiltration [CAVH]) or a blood pump (continuous venovenous hemofiltration [CVVH]) to continuously perfuse a large pore size dialysis membrane.
- **Indications:** To clear very large molecules, such as methotrexate, heparin, protamine, insulin, myoglobin, and antibiotics, especially vancomycin.
- **Complications:** Same as hemodialysis and secondary to anticoagulation; removal of beneficial therapeutic drugs = antibiotics, antidotes, vitamins.

Plasmapheresis

- **Mechanism:** To enhance elimination of large-molecular-weight compounds (greater than 15,000 Da) that are not dialyzable and have limited endogenous metabolism. Fresh frozen plasma (FFP) and albumin are used to replace removed plasma.

- **Indications:** To remove large protein-bound molecules, such as Ag/Ab complexes, especially digoxin-Fab complexes.
- **Complications:** Transfusion-related anaphylaxis or allergic manifestations.

Exchange Transfusion

- **Mechanism:** Same as plasmapheresis, but the replacement of removed blood is with packed red blood cells (PRBCs).
- **Indications:** Usually reserved for neonates.
- **Complications:** All transfusion related.

Physical, Diagnostic, and Laboratory Evaluation of the Poisoned Patient

Chapter Outline

Physical assessment of the poisoned patient

- Primary survey and treatment
- Secondary survey and treatment
- The unknown overdose
- Overdose in pregnancy
- Caustic cutaneous and ocular exposures

Pharmacokinetics

- Drug compartment models
- Drug elimination kinetics

Laboratory assessment of the poisoned patient

- Types of lab tests
- Testing methods (and degree of sensitivity and specificity, + to +++)
- Blood/serum levels
- Routine serum toxicology

Radiographic evaluation

- Visualizing toxins
- Toxin-induced skeletal changes
- Chest x-rays: Lungs
- Chest x-rays: Pleura, mediastinum, heart
- Abdominal x-rays
- Head computerized tomographic (CT) scan

Electrocardiographic (ECG) assessment

- Electrolyte and temperature disturbances
- Digitalis and tricyclic antidepressants (TCAs)
- Tachyarrhythmias and common causes
- Drug-induced tachycardias
- Drug-induced bradyarrhythmias

Nontoxic exposures

- Epidemiology of nontoxic exposures
- Categorizing nontoxic exposures
- Common nontoxic household exposures

Physical Assessment of the Poisoned Patient

Primary Survey and Treatment

Primary Survey

- Clear the airway.
- Assess and protect cervical spine.
- Intubate comatose patients for ventilation, lavage, and activated charcoal (AC) administration.
- Order arterial blood gas analysis and carboxyhemoglobin (COHb) level.
- Initiate electrocardiographic, temperature, oxygenation ($S_{TC}O_2$), and central and peripheral perfusion monitoring.
- Start IV, fluid load-normal saline or lactated Ringer's solution; draw complete blood count (CBC), glucose, electrolytes, BUN, creatinine, toxicology screen.
- Manage three seizure types: (1) benzodiazepine (BZ) responsive seizures — suspect ethanol withdrawal; (2) special antidote-required seizures — suspect pyridoxine or isoniazid (INH); (3) tonic-clonic seizures and/or persistent seizure activity on the electroencephalogram (EEG) — suspect carbon monoxide (CO).

Nonspecific Treatments = Coma Cocktail and Oxygen

- Dextrose: 0.5–1.0 g/kg; use $D_{50}W$ ($D_{10}W$ for children) to manage or exclude hypoglycemia.
- Thiamine: 100 mg IV to manage or prevent Wernicke-Korsakoff syndrome in alcohol abusers (unnecessary in children).
- Naloxone: 2 mg IV for both children and adults with opioid toxidromes.
- Oxygen at high flow rates, 8–10 L/min.

Secondary Survey and Treatment

Secondary Survey

- Exclude heart murmurs = suspect subacute bacterial endocarditis, common in intravenous drug users (cocaine and heroin).
- Exclude bradydysrhythmias and tachydysrhythmias = suspect digitalis, β -blockers, calcium channel blockers, tricyclic antidepressants.
- Exclude silent abdomen = suspect anticholinergics, opioids.
- Examine extremities for needle tracks (intravenous drug abusers) and evidence of heavy metal poisoning = Mees lines — arsenic, thallium; arsenical keratoses on hands and feet, arsenic-induced black foot's disease.

Secondary Treatment

- Gastric emptying: No emesis, orogastric lavage and initial AC with cathartic.
- Consider enhanced elimination beginning with MDAC.
- Consider other modalities of enhanced elimination.

The Unknown Overdose

Contraindicated Treatments

- No analeptics
- No flumazenil
- No forced diuresis
- No urinary acidification
- No Class IA or Class IC antiarrhythmics = all are sodium channel blockers that could prolong QRS duration and precipitate ventricular tachyarrhythmias, including torsades de pointes
- No long-acting opioid antagonists (only naloxone)

- Choose appropriate vasopressor support to avoid myocardial sensitization and arrhythmogenesis.

Alcohol and Drug Overdose

- Give coma cocktail.
- Monitor central venous pressure (CVP) and/or pulmonary artery pressure (PAP) prior to fluid loading and inotropic treatment.
- Suspect concomitant trauma. Head CT scan? Cervical spine films?
- Secure intensive care unit bed.
- Alcohol-smelling breath does not indicate intoxication; suspect combined etiologies. Patients with sole ethanol overdoses will awaken in 3 to 4 hours.

Overdose in Pregnancy

- Manage hypotension aggressively.
- Maintain left lateral decubitus position.
- Anticipate respiratory acidosis.
- Avoid unusual antidotes, except naloxone.
- Maintain high index of suspicion for carbon monoxide poisoning; measure carboxyhemoglobin (COHb) levels by co-oximetry; order hyperbaric oxygenation (HBO) for COHb levels greater than 15%.

- Normal pulse oximetry may be misleading; tissue hypoxia may be present with carbon monoxide (CO), cyanide (CN), and hydrogen sulfide (H₂S) poisoning despite normal pulse oximetry. Co-oximetry is indicated to exclude tissue hypoxia and cytotoxicity.

Caustic Cutaneous and Ocular Exposures

- **Skin:** (1) Personal protective equipment (PPE) for Emergency Medical Services (EMS) personnel — to prevent contamination and poisoning of EMS; (2) identify, remove, and bag all clothing and other personal items; (3) bathe patient with soap and water two times; (4) never try to neutralize acid or alkali burns; (5) do not apply topical creams or greases, as this may lead to prolonged contact with toxin with increased absorption and greater risk of burn injury.
- **Eye:** (1) Use topical anesthetic and lid retractor; (2) irrigate with 1 to 2 L sterile balanced salt solution (BSS) preferred over normal saline, lactated Ringer's solution, water irrigation; (3) apply pH strip to fornix to monitor and maintain pH 6.5 to 7.6. Alkalis cause liquefaction necrosis of lipoproteins and result in more severe conjunctival and mucosal burns than acids, which produce coagulation necrosis that blocks further tissue penetration.

Pharmacokinetics

Drug Compartment Models

- **One-compartment model:** Simple instantaneous equilibration model in which drug or toxin enters central circulatory compartment and is rapidly distributed to tissues, with plasma concentrations determining proportional changes in tissue concentrations. Example: ethanol.
- **Two-compartment model:** Most common model in which drug or toxin instantaneously distributes to two compartments — the more highly perfused central compartment and its viscera (brain, lungs, heart, liver, kidneys) and the less perfused tissue compartments (muscle, fat, skin). Example: barbiturates, volatile anesthetics.
- **Three- to five-compartment model:** Most complex model in which drug or toxin (especially heavy metals) distributes first to a central circulatory compartment, then to a highly perfused visceral compartment, and finally to the least perfused third compartment (bone, teeth, nails, hair). The soft tissue and bone compartments are often subdivided into labile and stable equilibrating subcompartments in a five-compartment model. Example: lead, cadmium.

Drug Elimination Kinetics

- **First-order:** The rate of a drug's elimination is directly proportional to its plasma concentration; a constant percentage of drug is eliminated per unit time. A plot of concentration vs. time is curvilinear. Example: most drugs.
- **Zero-order:** A constant amount of drug is eliminated per unit time, reflecting a saturation of the drug's metabolizing enzyme systems. Plot of concentration vs. time is linear. Example: alcohol.
- **Michaelis-Menten:** Drug elimination pattern changes from first-order to zero-order kinetics as drug concentration increases, reflecting gradual saturation of metabolizing pathways. Both plots of concentration vs. time are curvilinear.

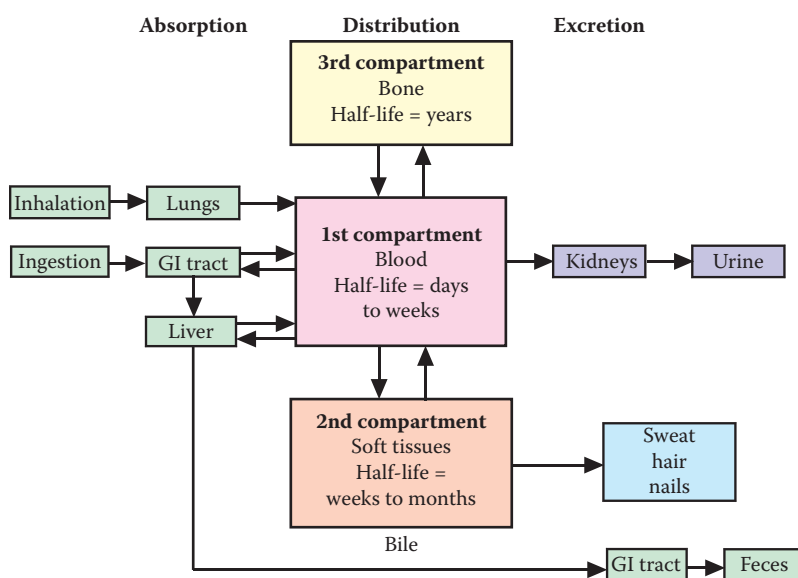


FIGURE 3.1 Ingested lead distributes in a three-compartment model. Ingested lead is distributed in a three-compartment model in which the heavy metal is initially distributed to a central circulatory compartment; then to a highly perfused visceral organ compartment; and finally to the least perfused third compartment composed of bone, teeth, nails, and hair.

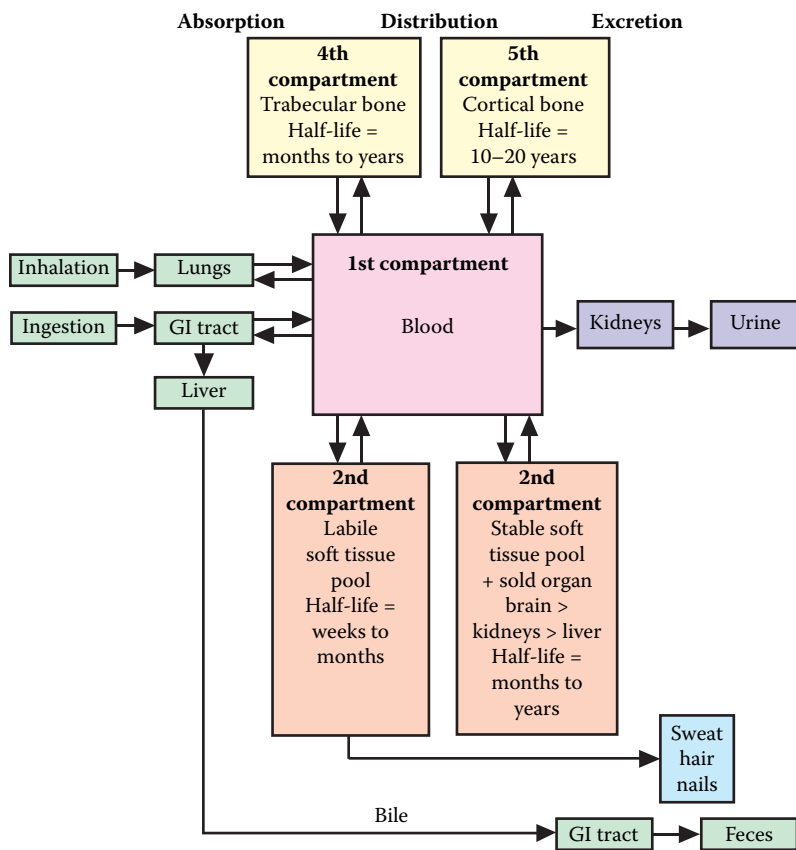


FIGURE 3.2 Ingested lead distributes in a five-compartment model. Ingested lead is distributed in a five-compartment model in which the heavy metal is initially distributed to a central circulatory compartment; then to a highly perfused visceral organ compartment; and finally to the least perfused third compartment composed of bone and soft tissues, subdivided into labile and stable subcompartments.

Laboratory Assessment of the Poisoned Patient

Types of Lab Tests

- **Monitoring:** Requires precision. Example: gentamicin levels.
- **Screening:** Requires sensitivity (Is a toxin present?). Example: employee urine drug tests.
- **Diagnostic:** Requires specificity (What is the toxin?). Example: forensic toxicology (tox) test.

Testing Methods (and Degree of Sensitivity and Specificity, + to +++)

Chemical Spot Tests (+)

- **Mechanism:** Identify the chemical reactivity, usually by a color change, between a drug and its specific reagent.
- **Indications:** Quick detection of single substances.
- **Example:** Urine ferric chloride test for aspirin.

Spectrophotometric Tests (+)

- **Mechanism:** Convert target drugs into identifiable light-absorbing compounds.
- **Indications:** Co-oximetry (for carbon monoxide, cyanide, and hydrogen sulfide poisoning) and colorimetry.
- **Example:** Carboxyhemoglobin (COHb) levels.

Immunoassays (++)

- **Mechanism:** Wide application; use drug-specific antibodies to identify toxic antigens, often using fluorescent polarization.
- **Indications:** Employee urine drug testing; affords rapid turn-around.

Chromatographic Assays

- **Thin-layer chromatography:** Drugs are spotted and coated onto plates, then recoated with silica gels for identification by unique properties.
- **High-pressure liquid chromatography:** Drugs are separated as liquids under high pressure within tightly packed columns for identification by unique properties.
- **Gas chromatography:** Drugs are extracted as gases at specific temperatures for identification by unique properties.
- **Gas chromatography/mass spectrometry GC/MS):** Highest sensitivity/specificity; effluent gases from initial gas chromatography are then ionized and separated by mass spectrometry. Example: opioid and amphetamine confirmation tests.

Blood/Serum Levels

Order for Diagnosis (Overdose Levels)

- Acetaminophen (>150 mcg/mL)
- Carbon monoxide (>15% COHb levels)
- Ethanol (>0.08–0.10%)
- Ethylene glycol (>25 mg/dL)
- Iron (>500 mcg/dL)
- Methanol (>25 mg/dL)
- Methemoglobin (MetHb) (>20–30% MetHb levels)
- Salicylate (>60 mg/dL)
- Theophylline (>90–100 mcg/mL)

Order for Treatment

- Therapeutic monitoring for all diagnostics, except ethanol
- Digoxin (>4 ng/mL)
- Heavy metals: arsenic, lead, mercury
- Lithium (>4 mEq/L)

- Organophosphates: Acetylcholinesterase (AChE) levels
- Phenobarbital (>100 mcg/ml)

Routine Serum Toxicology

Toxins Routinely Detected

- Alcohols
- Analgesics
- Antihistamines
- Antidepressants
- Barbiturates and sedatives
- Benzodiazepines
- Cardiovascular drugs
- Opioids and neuroleptics
- Miscellaneous: theophylline, caffeine, nicotine, sulfonyleureas, strychnine

Characteristics of Toxins Not Routinely Detected and Mechanisms of Nondetection

- **Too polar (highly water soluble):** Antibiotics, diuretics, ethylene glycol, isoniazid, lithium, metals.
- **Too nonpolar:** Digoxin, steroids.
- **Too volatile:** Anesthetics (nitrous oxide), hydrocarbons.
- **Too nonvolatile:** Plant alkaloids.
- **Too low:** Very potent drugs taken in small doses with resulting low serum concentrations — fentanyl, sufentanil, alfentanil, colchicine, lysergic acid diethylamide (LSD).
- **Too toxic:** Anions — bromide, cyanide, fluoride, nitrites.
- **Too new:** All new drugs whose unique physiochemical signatures have yet to be fully determined.

Radiographic Evaluation

Visualizing Toxins

Unknown Radiopaque Toxins

- Radiopacity = high physical density + high atomic number.
- Radiopaque medications will contain elemental constituents of atomic number greater than 15: most heavy metals, barium, bismuth, calcium, chlorine, iron, lead, potassium.
- CHIPS = anticipate radiopacity with: Chloral hydrate, heavy metals (As, Cd, Cr, Fe, Hg, Pb, Th, Tl), iron, phenothiazines, sustained-release, and enteric-coated tablets (ECTs).

Known Radiopaque Toxins

- **Iron:** Ferrous gluconate/sulfate.
- **Heavy metals:** As, Bi, Cd, Cr, Fe, Hg, Pb, Tl.
- **Toxins in radiopaque packets and containers:** Illicit packers and stuffers.
- **Mothballs:** Para-dichlorobenzene (densely radiopaque) > naphthalene > camphor (radiolucent).
- **Halogenated hydrocarbons:** More chlorine groups contribute to radiopacity — carbon tetrachloride (CCl₄), chloral hydrate, chloroform, halothane.



FIGURE 3.3 Bismuth subsalicylate (Pepto-Bismal®) abuse. Abdominal radiograph that demonstrates ascending right colon and transverse colon radiopaque substances in a patient with chronic bismuth subsalicylate abuse. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Decreased Bone Density

- **Corticosteroids:** Diffuse osteoporosis and focal osteonecrosis (avascular necrosis, especially of the femoral heads) (see Figure 3.5).
- **Adult hypervitaminosis D:** Diffuse osteoporosis.
- **Focal, lytic osteomyelitis:** Intravenous drug users (IVDUs) with septic emboli to sternum and sternoclavicular joints.
- **Distal acro-osteolysis:** Vinyl chloride monomer exposure.

Toxin-Induced Skeletal Changes

Increased Bone Density

- **Transverse metaphyseal bands on long bones:** Lead (arsenic) lines (see Figure 3.4).
- **Fluorosis (children and adults):** Ootosclerosis, osteophytosis, ligament calcifications.
- **Pediatric hypervitaminosis A:** Subperiosteal new bone and cortical hyperostosis.
- **Pediatric hypervitaminosis D:** Generalized ootosclerosis.



FIGURE 3.4 Metaphyseal “Lead Lines.” Frontal long bone radiograph of the legs of a 3.5-year-old girl with a chronic history of ingesting lead paint chips. Note the thickened, transverse, radiodense metaphyseal “lead (or arsenic) lines” and the widening of the metaphyses. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Chest X-Rays: Lungs

Airspace Filling

- **Diffuse filling:** Acute respiratory distress syndrome — noncardiogenic pulmonary edema = aspirin, opioids, cocaine (see Figure 3.6).
- **Diffuse filling:** Cardiogenic pulmonary edema = alcoholic and cobalt cardiomyopathy, barbiturate overdoses, cocaine cardiomyopathy.
- **Diffuse filling:** Cholinergic bronchorrhea = organophosphate and carbamate pesticides, inhalants, low solubility gases (nitrogen dioxide, phosgene).
- **Focal filling:** Aspiration, especially hydrocarbons.



FIGURE 3.5 Steroid-induced osteonecrosis. Coronal magnetic resonance (MRI) of the left hip in a patient on chronic corticosteroid therapy that demonstrates the characteristic “double line” sign of steroid-induced osteonecrosis with inner and outer hyperintense rim lines. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

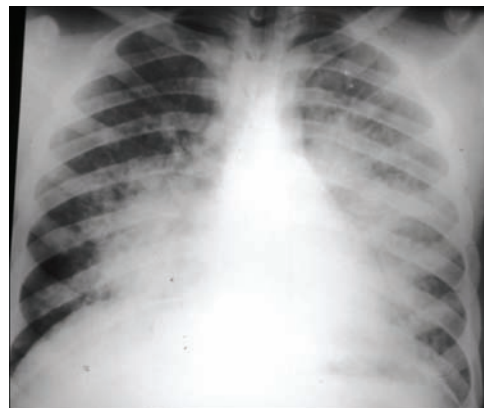


FIGURE 3.6 Non-Cardiogenic Pulmonary Edema: Heroin Overdose. Frontal chest radiograph that demonstrates normal size and configuration of the cardiomeastinal silhouette with diffuse bilateral non-cardiogenic pulmonary edema following heroin overdose. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Interstitial Patterns

- **Reticulonodular pattern:** Hypersensitivity pneumonitis (sulfa drugs — nitrofurantoin) and allergic alveolitis (farmer's lung, bagassosis).
- **Interstitial fibrosis:** Cytotoxic chemotherapeutics (busulfan, bleomycin, methotrexate, cyclophosphamide).
- **Phospholipidosis:** Amiodarone; injected particles in IVDUs from adulterated cocaine and heroin powders — talcosis from adulterated cocaine and heroin powders.
- **Pneumoconioses:** Asbestos, beryllium, coal, silica.

Chest X-Rays: Pleura, Mediastinum, Heart

- **Pleural effusions:** Drug-induced lupus syndromes = hydralazine and procainamide; isoniazid, methyldopa, chlorpropamide.
- **Pneumomediastinum:** Caustic-induced esophageal perforation, ipecac- or alcohol-induced Mallory-Weiss syndrome.
- **Pleural plaques:** Asbestosis.
- **Hilar lymphadenopathy:** Phenytoin, anthrax.
- **Cardiomegaly:** Alcoholic and cobalt cardiomyopathy, cardiotoxic chemotherapeutics = adriamycin.
- **Aortic dissection:** Cocaine.

Abdominal X-Rays

- **Pneumoperitoneum:** Secondary to gastrointestinal perforation = caustics (acids, alkalis, iron), cocaine, ipecac, lavage tube.
- **Mechanical obstruction:** Secondary to gastric outlet bezoars, or small bowel obstruction = enteric-coated tablets, concretions, body packers and stuffers (see Figure 3.9).
- **Ileus:** Secondary to decreased gastrointestinal motility = anticholinergics, antihistamines, tricyclic antidepressants (TCAs), opioids, ischemic bowel (cocaine, oral contraceptives), hypokalemia, hypomagnesemia.
- **Intramural gas:** Secondary to intestinal vasospasm, thrombosis, infarction = cocaine, ergots, oral contraceptives, clostridium derfringens toxin-induced pneumatosis intestinalis (pigbel).

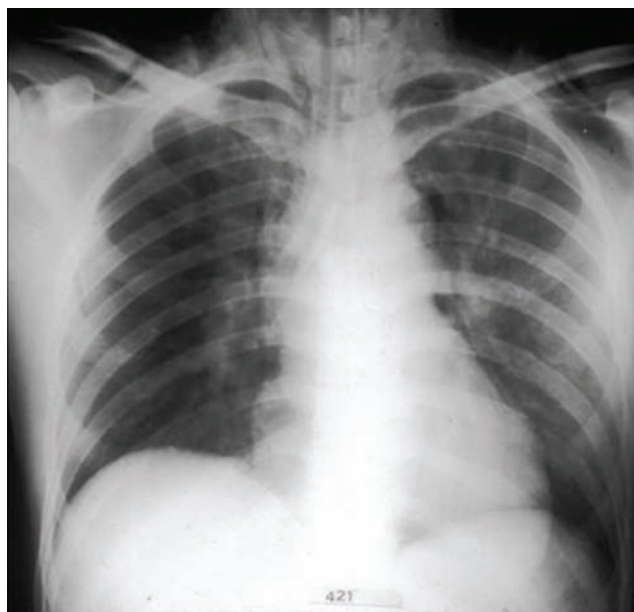


FIGURE 3.7 Pneumomediastinum: crack-cocaine inhalation. Frontal chest radiograph that demonstrates abnormal scattered radiolucencies in the mediastinum and base of neck consistent with pneumomediastinum and cervical subcutaneous emphysema following crack-cocaine inhalation. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)



FIGURE 3.8 Cocaine-induced acute aortic dissection. Sagittal, oblique, T-1 weighted magnetic resonance image (MRI) of the chest demonstrating an intimal flap that divides the lumen of the descending aorta into a false lumen and a true lumen with blood flow, consistent with acute thoracic aortic dissection Type B in an intravenous crack-cocaine abuser. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

- Radiodense foreign bodies = bismuth subsalicylate, calcium carbonate, clay (pica), iron and other heavy metals, especially lead.

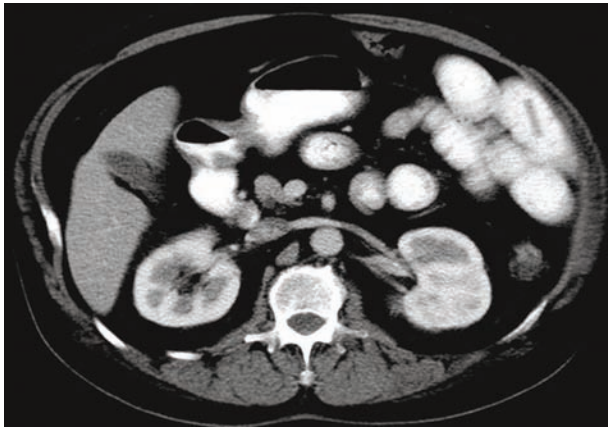


FIGURE 3.9 Body stuffer: heroin. Axial abdominal oral and intravenous contrast-enhanced computerized tomogram (CT) at the level of the renal veins that demonstrated a rectangular container of heroin in a jejunal loop. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

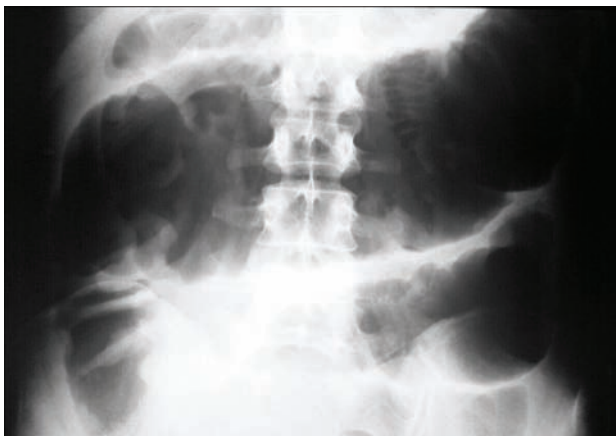


FIGURE 3.10 Opioid bowel: colonic ileus in a methadone abuser. Abdominal radiograph (KUB) that demonstrates air distension of the small bowel and transverse colon consistent with chronic constipation and colonic ileus in a methadone abuser. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)



FIGURE 3.11 Cocaine-induced intestinal ischemia. Abdominal radiograph (KUB) demonstrating gas in the main portal vein and its intrahepatic primary and secondary branches with diffuse dilation and pneumatosis intestinalis of the small bowel and colon in a chronic cocaine abuser with acute mesenteric ischemia and multiple small bowel infarctions. Chronic ergot alkaloid ingestion may also be associated with acute mesenteric ischemia and small bowel infarction. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Head Computerized Tomographic (CT) Scan

- **Intracranial hemorrhage:** Suspect intraparenchymal cerebrovascular accident or subarachnoid hemorrhage = amphetamines, cocaine, ephedrine and pseudoephedrine, phenylpropanolamine, phencyclidine (PCP); or subdural = head trauma (alcohol, sedative-hypnotics, seizures).
- **Lucencies:** Suspect basal ganglia necrosis = carbon monoxide, cyanide, hydrogen sulfide (H_2S), methanol; suspect vasospasm = cocaine, ergots; septic emboli = intravenous drug users (IVDUs).
- **Atrophy:** Cerebral and cerebellar atrophy = alcohol and toluene.
- **Calcifications:** Basal ganglia = carbon monoxide and lead.



FIGURE 3.12 Subarachnoid hemorrhage: intravenous cocaine abuse. Cranial computerized axial tomogram (CT) at the level of the pons that demonstrates acute blood hyperdensities in the suprachiasmatic cistern extending into the left Sylvian fissure, consistent with acute subarachnoid hemorrhage following intravenous cocaine overdose. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Electrocardiographic (ECG) Assessment

Electrolyte and Temperature Disturbances

Electrolyte Disturbances

- **Hyperkalemia:** Tall tented T waves with progressive widening of the QRS complex (see Figure 3.13a).
- **Hypokalemia:** Progressive decrease in T wave amplitude with inverted T waves, U waves, and eventual fusion of T and U waves (see Figure 3.13b).
- **Hypercalcemia:** Short QT and ST intervals = antacids, vitamins A and D, hydrochlorothiazide (HCTZ) containing diuretics (see Figure 3.14a).
- **Hypocalcemia:** Prolonged QT and ST intervals = fluoride, hydrofluoric acid, calcitonin, ethylene glycol, phosphates (see Figure 3.14b).

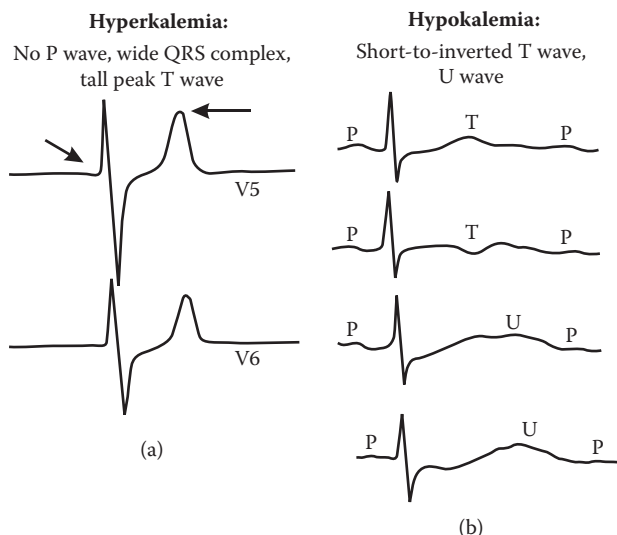


FIGURE 3.13 (a) Electrocardiographic evidence of hyperkalemia. Electrocardiogram (ECG) Lead II tracing in a patient with hyperkalemia that demonstrates no P wave, wide QRS complex, and a tall peaked T wave. (b) Electrocardiographic Evidence of Hypokalemia. Electrocardiogram (ECG) Lead II tracing in a patient with hypokalemia that demonstrates short-to-inverted T waves and U waves

Hypothermia Disturbances

- Progressive conduction block
- Progressive sinus bradycardia
- Prolonged PR and QT intervals
- Progressive widening of the QRS complex with the J wave of Osborn, located in the terminal phase of the QRS complex
- Causes: Drugs causing CNS depression (ethanol, opioids, imidazolines, sedative-hypnotics) or hypoglycemia (insulin, oral hypoglycemics)

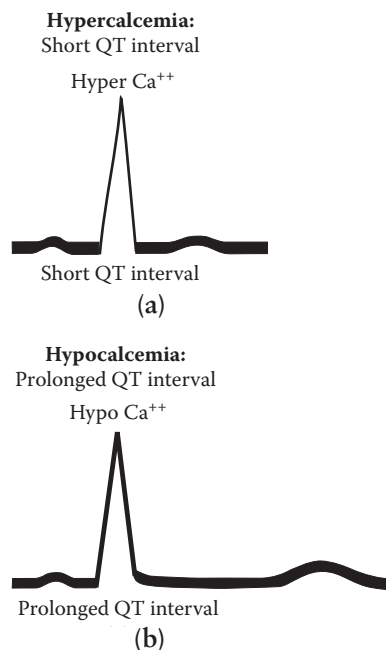


FIGURE 3.14 (a) Electrocardiographic evidence of hypercalcemia. Electrocardiogram (ECG) Lead II tracing in a patient with hypercalcemia that demonstrates a short QT interval (b) Electrocardiographic Evidence of Hypocalcemia Caption. Electrocardiogram (ECG) Lead II tracing in a patient with hypocalcemia that demonstrates a prolonged QT interval.

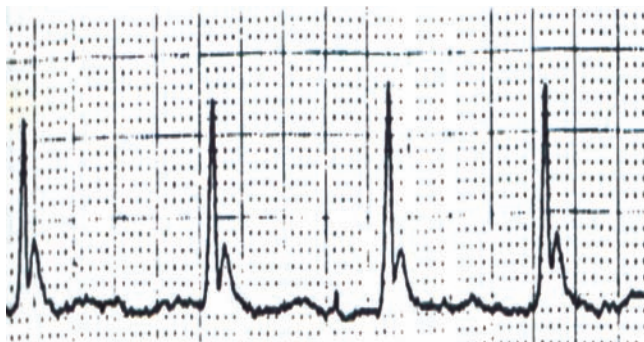


FIGURE 3.15 Electrocardiographic evidence of hypothermia. Top figure: The ECG J wave trace on the ECG graph paper. Bottom figure: The annotated J wave with the J wave trace with the J waves pointed out by arrows.

Hypothermia ($\geq 24^{\circ}\text{C}$ rectally): note the characteristic **J Wave of Osborn** in the terminal phase of the QRS complex.



FIGURE 3.16a Electrocardiographic evidence of digoxin toxicity. Electrocardiogram (ECG) Lead II tracing in a patient with digoxin toxicity that demonstrates atrial tachycardia and atrioventricular conduction block.

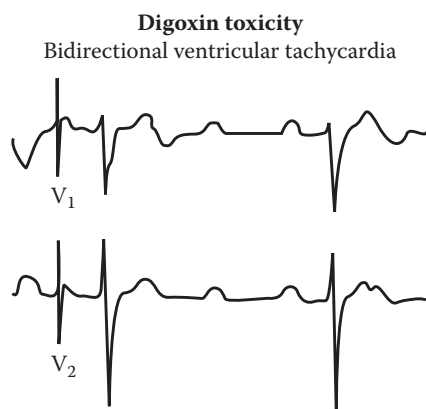


FIGURE 3.16b Electrocardiographic evidence of digoxin toxicity. Electrocardiogram (ECG) Lead II tracing in a patient with digoxin toxicity that demonstrates bi-directional ventricular tachycardia, pathognomonic of digoxin toxicity.

Digitalis and Tricyclic Antidepressants (TCAs)

Digitalis (Digoxin) Effects

- Initial ectopic rhythms and premature ventricular contractions (PVCs) (10–15%)
- Progressive bradycardia
- Increased PR interval progressing to atrioventricular (AV) blocks (see Figure 3.16a)
- Extrasystoles leading to tachyarrhythmias
- Pathognomonic bi-directional ventricular tachycardia (see Figure 3.16b)

TCA Effects

- Sinus tachycardia
- Prolonged PR, QRS, QT intervals
- AV and bundle branch blocks
- Prominent S waves in lead I and AVL, prominent R wave in AVR
- All supraventricular and ventricular arrhythmias, including torsades de pointes
- Asystole

Tachyarrhythmias and Common Causes

- **Anticholinergics and antihistamines:** Block fast inward sodium channels, like quinidine, and amide local anesthetics (LAs).
- **Adrenergic agonists:** Increase cyclic adenosine monophosphate (AMP) = all β_2 -agonists.
- **Phosphodiesterase inhibitors:** Increase cyclic AMP = methylxanthines (theophylline, caffeine, theobromine) and amrinone; all can cause

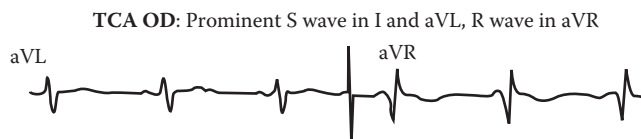


FIGURE 3.17 Electrocardiographic evidence of tricyclic antidepressant overdose. Electrocardiogram (ECG) tracing in a patient with a history of suicide attempt by tricyclic antidepressant overdose that demonstrates a prominent S wave in Lead I and AVL, a prominent R wave in AVR, and widened QRS complexes indicative of cardiac sodium channel blockage that should correct with intravenous sodium bicarbonate administration.

supraventricular tachyarrhythmias (SVT), atrial fibrillation (Afib), atrial flutter (AF).

- **Diet pills:** Amphetamine and serotonin effects can cause pulmonary hypertension = phen-termine, fenfluramine, dextroamphetamine, sibutramine.
- **Botanicals:** Sympathomimetics = khat, betel nut, ginseng (Ginseng Abuse Syndrome [GAS]: tachycardia, hypertension, insomnia, morning diarrhea).
- **Thyroid hormone:** Sinus tachycardia.
- **Metals:** Arsenic (As) = increased QT intervals and torsades de pointes; lithium = mimics hypokalemia.

Drug-Induced Tachycardias

Theophylline Overdose: Supraventricular Tachycardia

Astemizole/terfenadine overdose or CYP 3A4 Interactions: torsades de pointes, prolonged QT intervals, and VT.

Prolonged QT Intervals and Torsades de Pointes

- **Milieu:** Hypokalemia, hypomagnesemia, hypocalcemia; preexisting bradycardia, ischemia, or hypoxia.
- **Toxins:** Non-sedating antihistamines = astemizole and terfenadine; pentamidine; arsenic.

Ventricular Tachycardia (VT)

- Chloral hydrate and all halogenated hydrocarbons that sensitize the myocardium to exogenous and endogenous catecholamines.
- **Propoxyphene:** Junctional tachycardia, widening QRS complex → VT.
- **Phenothiazines:** Quinidine-LA effects = prolonged QT interval and widened QRS complex → VT.
- **Chloroquine:** Also has quinidine-like effects = prolonged QT intervals → VT.
- **Amantadine:** Blocks dopamine re-uptake, prolonged QT interval → VT.
- **Botanicals:** Monkshood = digitalis and vagomimetic effects; yew = digitalis effects, heart blocks, and VT possible.



FIGURE 3.18 Electrocardiographic Evidence of Chloral Hydrate Toxicity. Electrocardiogram (ECG) tracing in a patient sedated with oral chloral hydrate for a magnetic resonance imaging procedure that demonstrates the ventricular ectopic or premature beats (premature ventricular contractions) characteristic of chlorinated hydrocarbon toxicity from chloral hydrate or halogenated hydrocarbon anesthetics (halothane and others) with myocardial sensitization to endogenous catecholamines

Drug-Induced Bradyarrhythmias

- **Calcium channel blockers:** Decreased inotropy and AV conduction, smooth muscle vasodilation, progressive AV blocks.
- **Beta-blockers:** Type IA or quinidine-like effects, mimic calcium channel blockers (CCBs), with progressive bradycardia, AV blocks, complete heart block.
- **Ischemia:** ST segment and T wave changes, Q myocardial injury waves from hypotension, coronary vasospasm, hypoxia = cocaine and ergot alkaloids.

Nontoxic Exposures

Epidemiology of Nontoxic Exposures

More than 40% of poison exposures reported to Poison Control Centers are nontoxic exposures.

Nontoxic exposures fall into two categories: (1) exposures to products unlikely to cause toxicity at any dose; and (2) exposures to products that are potential toxins, but at doses that are nontoxic (e.g., acetaminophen ingestions of <150 mcg/kg).

Categorizing Nontoxic Exposures

- The product must be absolutely identified.
- There is only a single product exposure.
- The exposure must be unintentional.
- Consumer Product Safety Commission (CPSC) warnings must not appear on labels: Caution, Warning, Danger!
- A reliable approximation of the amount (dose/kg) of exposure must be determined.
- The route of exposure must be assured by history.
- The exposed patient is symptom-free.
- Follow-up consultation must be available.

Common Nontoxic Household Exposures

TABLE 3.1 Nontoxic Home Products

Personal-Use Items	Art Supplies	Toys
Bath products, deodorants	Charcoal, chalk, clay, crayon	Bath toys
Shampoos, lotions	Latex paints	Caps
Cosmetics	Pens, pencils	Etch-a-Sketch®
Colognes	Glues	Play-Doh®
Hairsprays	Pastes	Toy cosmetics
Toothpastes	Watercolors	Teething rings

TABLE 3.2 Nontoxic Home Products

Medications	Cleansers	Miscellaneous
Antacids, antibiotics	Fabric softeners	Matches, candles
Oral contraceptives, steroids	Bleach, 2–5%	Newspaper
Calamine lotion	Detergents	Grease, motor oils
Mineral oil	Most soaps	Incense, putty
Zinc and zirconium oxide	Dishwasher liquids	Spackle, silica gels

Antidotes

Chapter Outline

Toxidromes and antidotes

Toxidromes: Parasympathetic
Toxidromes: Sympathetic
Toxidromes: Central nervous system (CNS)
Toxidromes: Opioid

Gastrointestinal decontaminants

Decontamination: Activated charcoal (AC)
Decontamination: Multi-dose AC (MDAC)
Decontamination: Cathartics
Diluents and neutralizers
Decontamination: Ipecac
Decontamination: Whole-bowel irrigation (WBI)

Metal chelators

Chelators: Calcium disodium edetate (CaNa_2EDTA)
Chelators: Deferoxamine
Chelators: British anti-Lewisite (BAL)
Chelators: Succimer (dimethylsuccinic acid — DMSA)
Chelators: D-penicillamine

Antivenins and antitoxins

Crotalid antivenins
Elapid antivenins
Centruroides antivenins
Latrodectus antivenins
Botulinum antitoxin
Digoxin-specific Fab (Antibody fragment, antigen-binding)

Specific antagonists

Calcium channel blocker antagonist: Calcium
Benzodiazepine antagonist: Flumazenil
Opioid antagonists
Anticholinesterase (AChE) antagonist:
Physostigmine
Heparin antagonist: Protamine

Vitamins

Folic and folinic acids
Hydroxocobalamin (vitamin B_{12} precursor)
Vitamin K (vitamin K_1)

Pyridoxine (vitamin B_6)
Thiamine (vitamin B_1)
Niacin (nicotinic acid) and niacinamide (nicotinamide)

Specific antidotes

Ethanol
Fomepizole (4-methylpyrazole)
n-Acetylcysteine (NAC)
Pralidoxime (2-PAM)
Miscellaneous specific antidotes

Nonspecific antidotes

Dextrose
Glucagon
Methylene blue
Cyanide Antidote Kit®
Sodium bicarbonate
Hyperbaric oxygen (HBO) therapy
HBO: CO poisoning

Toxidromes and Antidotes

Toxidromes: Parasympathetic

Anticholinergic Toxidrome

- **Features:** “Blind as a bat, hot as Hades, red as a beet, dry as a bone, mad as a hatter” = dilated pupils, cycloplegia, flushed dry skin, fever, thirst, exocrine gland hyposecretion, decreased bowel sounds, urinary retention, tachycardia, delirium.
- **Causes:** Belladonna alkaloids, antihistamines, tricyclic antidepressants (TCAs), antipsychotics, anti-Parkinson drugs, jimson weed (*Datura stramonium*), *Amanita muscaria*.
- **Antidote:** Physostigmine.

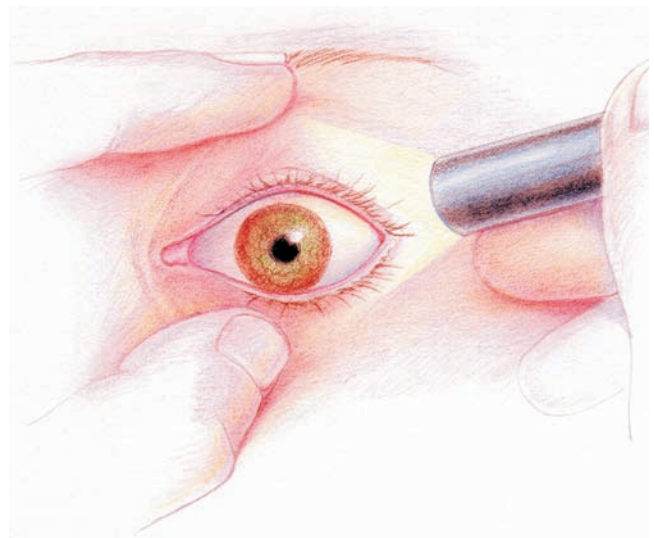


Figure 4.1 Mydriasis, left eye. Pupillary dilation or mydriasis characteristic of an anticholinergic toxidrome.

Cholinergic Toxidrome

- **Features:**
 - SLUDE = Muscarinic features: Salivation, Lacrimation, Urination, Defecation, Emesis, plus miosis, bronchorrhea and bronchospasm = DUMBBELS = Diarrhea, Urination, Miosis, Bronchorrhea, Bronchospasm, Emesis, Lacrimation, and Salivation.
 - Nicotinic features: Weakness, fasciculations, sweating, tachycardia, hypertension.
 - CNS features: Agitation/confusion, seizures, coma.
- **Causes:** Organophosphates, carbamates and “stigmines” (neostigmine, physostigmine, pyridostigmine, edrophonium), nerve gases, echothiophate = anticholinesterase (AChE) inhibitors; pilocarpine; Clitocybe/Inocybe mushrooms.
- **Antidote:** Atropine +/- pralidoxime.



Figure 4.2 Miosis, left eye. Pupillary constriction or miosis characteristic of cholinergic and opioid toxidromes.

Toxidromes: Sympathetic

Sympathomimetic Toxidrome

- **Features:** “*Fight or flight*” = hypertension, tachycardia, sweating, fever, excitation-psychomotor agitation, tremor, seizures, dilated pupils.
- **Causes:** Amphetamines/diet drugs, cocaine, theophylline, caffeine, methylphenidate, monoamine oxidase inhibitors; over-the-counter cold medications, especially those containing phenylpropanolamine (PPA), ephedrine, and pseudoephedrine.
- **Mechanisms:** Increased release of catecholamines (amphetamines), blockade of catecholamine re-uptake (cocaine), inhibition of catecholamine metabolism (monoamine oxidase inhibitors), indirect adrenergic receptor stimulation (ephedrine).
- **Antidote:** Beta-blockers.

Hypermetabolic Toxidrome

- **Features:** “*Uncoupling of oxidative phosphorylation*” = fever, tachycardia, hyperpnea, tachypnea, restlessness, convulsions, combined metabolic acidosis and respiratory alkalosis.
- **Causes:** Salicylates (ASA), chlorophenoxyacetic acid herbicides (2,4-D and 3,4,5-T), triethyl tin, some phenols (e.g., nitrophenol).
- **Antidote:** Lavage and activated charcoal, supportive.

Toxidromes: Central Nervous System (CNS)

Benzodiazepine Toxidrome

- **Features:** “*Coma with stable vital signs*” = mild sedation-to-complete unresponsiveness, amnesia, respiratory depression, loss of airway protective reflexes, hypotension.
- **Causes:** Benzodiazepines.
- **Antidote:** Physostigmine.

Extrapyramidal Toxidrome

- **Features:** “*Drug-induced parkinsonism*” = tremor, rigidity, opisthotonus, torticollis, dysphonia, oculogyric crisis = tardive dyskinesias.
- **Causes:** Phenothiazines, butyrophenones (haloperidol, droperidol), metoclopramide, clomipramine.
- **Antidote:** Diphenhydramine.

Toxidromes: Opioid

Opioid Toxidrome

- **Features:** Pinpoint pupils, somnolence, CNS depression, respiratory depression, bradycardia, hypotension, hypothermia, decreased gastrointestinal motility, constipation.
- **Causes:** All opioids, natural and synthetic, including propoxyphene, tramadol, codeine, dextromethorphan. Exception: imidazolines, central alpha agonists = clonidine, oxymetazoline, and tetrahydrolozinE.
- **Antidote:** Naloxone.

Withdrawal Toxidrome

- **Features:** Yawning, sneezing, runny nose, lacrimation, “goose bumps,” abdominal cramps, diarrhea, restlessness, hallucinations, tachycardia, and hypertension.
- **Causes:** Opioid, alcohol, barbiturate, benzodiazepine cessation/withdrawal.
- **Antidote:** “Cold turkey,” agonists as substitutes (e.g., methadone, clonidine), antagonists for maintenance (naltrexone), aversives (disulfiram) pose increased risks.

Gastrointestinal Decontaminants

Decontamination: Activated Charcoal (AC)

Properties

- **Chemistry:** Pyrolyzed carbonaceous materials, steam — and then CO_2 — activated to create pores and increases adsorptive surface area (1000–2000 M^2).
- **Mechanism:** Adsorption by H_2 ion bonding and van der Waals forces of agents that are nonionized, undissociated, not protein-bound, poorly/slowly absorbed and distributed or retained in the gastrointestinal tract by reduced gut motility (often secondary to anticholinergics and opioids).
- **Contraindications:** Coma, seizure, vomiting, ileus, small bowel obstruction (SBO), simultaneous whole-bowel irrigation (WBI) with polyethylene glycol (PEG) administration; ingestions of alcohols, hydrocarbons (HCs), metals, caustics, lithium.

Applications

- **Use:** Most organic and inorganic materials, ASA, acetaminophen, barbiturates, glutethamide, phenytoin, theophylline, TCAs.
- **Dose:** Early (within 1–4 hours) administration of a flavored 8:1 water slurry, 10:1 AC drug, 1–2 g/kg body weight (bw).
- **Side effects:** Vomiting, aspiration, diarrhea, later constipation, possibly small bowel obstruction (SBO); AC is usually combined with a cathartic, particularly 70% sorbitol preferred over Mg citrate.

Decontamination: Multi-Dose AC (MDAC)

Properties

- **Chemistry:** Provides constant intestinal clearance by maintaining a continuous diffusion

gradient between blood and gut (known as gut dialysis).

- **Mechanism:** Gastrointestinal tract dialysis, especially for large ingestions, enteric, or slow/sustained release drug ingestions, to halt enterohepatic circulation of poisons.
- **Contraindications:** Same as AC — coma, seizure, vomiting, ileus, SBO, simultaneous WBI; ingestions of alcohols, HCs, metals, caustics, lithium.

Applications

- **Uses:** Digoxin, phenobarbital, carbamazepine, phenylbutazone, dapsone, methotrexate, naldolol, theophylline, ASA, TCAs, cyclosporine, propoxyphene.
- **Dose:** 0.25–0.5 g/kg q 2–6 hours, starting within 1 hour of ingestion.
- **Side effects:** Same as AC — vomiting, aspiration, diarrhea, later constipation, possibly SBO; add a cathartic only to first dose of AC.

Decontamination: Cathartics

Properties

- **Chemistry:** Saline and glucose-based cathartics composed of nonabsorbable cations (Mg, Na) that establish an osmotic gradient to draw water into gut.
- **Mechanism:** Magnesium citrate and sorbitol are osmotic cathartics.
- **Contraindications:** Adynamic ileus — SBO, abdominal trauma, diarrhea, renal failure (Mg citrate), more than initial dose of MDAC. Oil-based cathartics (mineral oil) are hydrocarbons (HCs), increase aspiration risk, and increase HC and mothball absorption.

Applications

- **Use:** To reduce constipation with possible SBO from AC, to speed delivery of AC to small intestine (SI), and to speed fecal elimination of poorly absorbed, sustained-release, or enterohepatically recirculated toxins.
- **Dose:** Sorbitol 0.5–1.0 g/kg; Mg citrate 4 mL/kg.
- **Side effects:** Nausea, vomiting, diarrhea, abdominal cramping, dehydration-hypovolemia, hyponatremia, hypokalemia, hyponatremic-hypokalemic metabolic alkalosis (Mg citrate), hypernatremic dehydration (sorbitol).

Diluents and Neutralizers

Properties of Diluents

- **Chemistry:** Water or milk to dilute ingested alkalis or weak acids.
- **Mechanism:** Reduce caustic contact time with gastrointestinal mucosa, modify and reduce the heat dissipated by the initial hydration and subsequent neutralization of the caustic at tissue (mucosal) expense.
- **Contraindications:** All noncaustics and strong acids (Exception: HCl — careful removal via nasogastric (NG) may be indicated). Neutralization of caustics is not recommended, except for nebulized sodium bicarbonate (NaHCO_3) following chlorine and chloramine gas inhalation.

Applications of Diluents

- **Use:** Dilution of alkalis and weak acids (e.g., milk for ingested fluoride or hydrofluoric acid [Ca gluconate preferred]).
- **Dose:** Water or milk, 250 mL orally (po), or 15 mL/kg of body weight (bw).
- **Side effects:** Could increase heat production by water contact — increases hydration and neutralization reactions; acute gastric distension with potential for vomiting and aspiration of caustics.

Decontamination: Ipecac

Properties

- **Chemistry:** A *Cephaelis* spp. plant extract containing two powerful emetic plant alkaloids: (1) cephaline more than (2) emetine.
- **Mechanism:** (1) Local activation of peripheral sensory receptors in the first part of the duodenum; (2) central stimulation of the chemoreceptor trigger zone (CTZ) by cephaline.
- **Contraindications:** All HC and caustic ingestions, altered mental status, poor airway protective reflexes (aspiration risk); bleeding diathesis; sharp object and battery ingestions.

Applications

- **Use:** Best for *at-home* use immediately after (less than 30 minutes) ingestions without additional oral fluids.
- **Dose:** 15 mL (1 Tbsp.) for children, 30 mL (2 Tbsp.) for adults, may repeat once in 30 minutes.
- **Side effects:** Delays administration of AC or specific antidote therapy in the emergency department (ED), vagal bradycardia, prolonged vomiting with Mallory-Weiss esophageal tears, rarely cerebrovascular accident (CVA) in adults.

Decontamination: Whole-Bowel Irrigation (WBI)

Properties

- **Chemistry:** A nonabsorbable mixture of polyethylene glycol (PEG) and electrolyte lavage solution (ELS) to fluid flush the gut.
- **Mechanism:** To flush out the entire gastrointestinal tract without causing fluid and electrolyte shifts to reduce the mucosal contact time available for poison absorption.
- **Contraindications:** Any preexisting gastrointestinal pathology-ileus, SBO, gastrointestinal perforation.

Applications

- **Use:** All sustained-release drug ingestions (theophylline, verapamil, fenfluramine); all poisons unabsorbed by AC (iron, lead, zinc, lithium); and for all body packers.
- **Dose:** 0.5 L/h for children, 2 L/h for adults orally (po) or NG for 4–6 hours.
- **Side effects:** Gastric distension and vomiting (add an antiemetic), anal itching.

Metal Chelators

Chelators: Calcium Disodium Edetate (CaNa₂ EDTA)

Properties

- **Chemistry:** Water-soluble, calcium-containing ring-structured acid.
- **Mechanism:** Exchanges its ring-bound Ca for most heavy metals, usually lead, to form a stable, nonionized, water-soluble chelate that can be renally excreted.
- **Contraindications:** Dehydration, renal dysfunction, coronary artery disease (CAD) chelation, sole therapy (without BAL initially) in lead encephalopathy — give BAL first, then EDTA 4 hours later to decrease brain lead delivery.

Applications

- **Use:** To chelate lead in lead poisoning; in conjunction with BAL initially to rapidly chelate lead in lead encephalopathy.
- **Dose:** IM in procaine or IV (preferred) diluted in normal saline over 8 to 24 hours.
- **Side effects:** Chelation and subsequent depletion of essential metals (Cu, Fe, Mn, Zn); elevated liver function tests (LFTs); calcinosis at injection sites; thrombophlebitis; nephrotoxicity from lead release in kidneys during excretion.

Chelators: Deferoxamine

Properties

- **Chemistry:** A water-soluble, specific iron chelator created by removing ferric iron (Fe³⁺) from ferrioximine.
- **Mechanism:** Chelates free iron and iron in transit between transferrin and ferritin; but will not chelate iron complexed to hemoglobin (Hb), ferritin, or hemosiderin.
- **Contraindications:** None.

Applications

- **Use:** To chelate iron in iron overdose, massive transfusions, hemosiderosis, and thalassemia; to chelate aluminum (Al) in chronic renal failure (CRF).
- **Dose:** 1 g IM, then 0.5 g q 4–12 hours; IV 15 mg/kg/min slowly.
- **Side effects:** Decreases blood pressure; pulmonary toxicity (ARDS); oculotoxicity (decreased vision, decreased color vision, night blindness); and ototoxicity (deafness). Acts as a siderophore for some bacteria that cannot absorb iron — *Yersinia enterocolitica* and *Vibrio* species. Increased *V. vulnificus* sepsis risks. Rose-orange colored urine.

Chelators: British Anti-Lewisite (BAL)

Properties

- **Chemistry:** Nonspecific metal chelator formulated in peanut oil and developed during World War II as an antidote for Lewisite (arsine) and mustard vesicant gases.
- **Mechanism:** A sulfur-donating chelator that forms stable bonds with soft metals, especially As and Hg. Can also bind borderline soft metals, particularly lead.
- **Contraindications:** Peanut allergy, liver dysfunction, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency (hemolytic anemia), organic or methyl Hg poisoning.

Applications

- **Use:** To chelate As, elemental and inorganic Hg; to treat arsenical dermatitis; to use in conjunction with EDTA as initial chelation in lead encephalopathy.
- **Dose:** Deep IM 2.5 mg/kg q 4–6 hours × 4 doses; topical application for mustard gas.
- **Side effects:** Local injection site pain, fever, hypertension, tachycardia, nausea, vomiting,

headache. Can also chelate essential metals (especially Cu and Zn) and will chelate iron during concomitant iron therapy.

Chelators: Succimer (Dimethylsuccinic Acid — DMSA)

Properties

- **Chemistry:** A more water-soluble analog of BAL that is less toxic and more specific for lead, a borderline soft metal, than BAL.
- **Mechanism:** Same as BAL, but less toxic, effective orally, will not chelate essential metals (Cu, Fe, Mn, Zn), and can be used with concomitant iron therapy. Succimer does not cause hemolysis in G-6-PD deficiency.
- **Contraindications:** None.

Applications

- **Use:** Lead poisoning (BPb greater than 45 mcg/dL), unapproved for organic and inorganic Hg poisoning and As poisoning.
- **Dose:** 30 mg/kg/day orally for five (5) doses.

- **Side effects:** Transient increases in liver enzymes (AST) and multiple abdominal complaints — crampy abdominal pain, flatus, and diarrhea.

Chelators: D-Penicillamine

Properties

- **Chemistry:** A highly toxic, penicillin-derived, nonspecific metal chelator (Cu > As, Hg, Pb) that is orally titrated over weeks.
- **Mechanism:** Same as succimer, but less effective and has more side effects; works best for Cu.
- **Contraindications:** Penicillin allergy, preexisting skin diseases, or renal dysfunction.

Applications

- **Uses:** Cu chelation in Wilson's disease (hepatolenticular degeneration).
- **Dose:** 10 mg/kg/day orally, increased by 10 mg/kg/week to 30 mg/kg/day over 10 weeks.
- **Side effects:** Severe nausea and vomiting, leukopenia, thrombocytopenia, eosinophilia, aplastic anemia, myopathy, dermatitis — Stevens-Johnson syndrome, nephrotic syndrome.

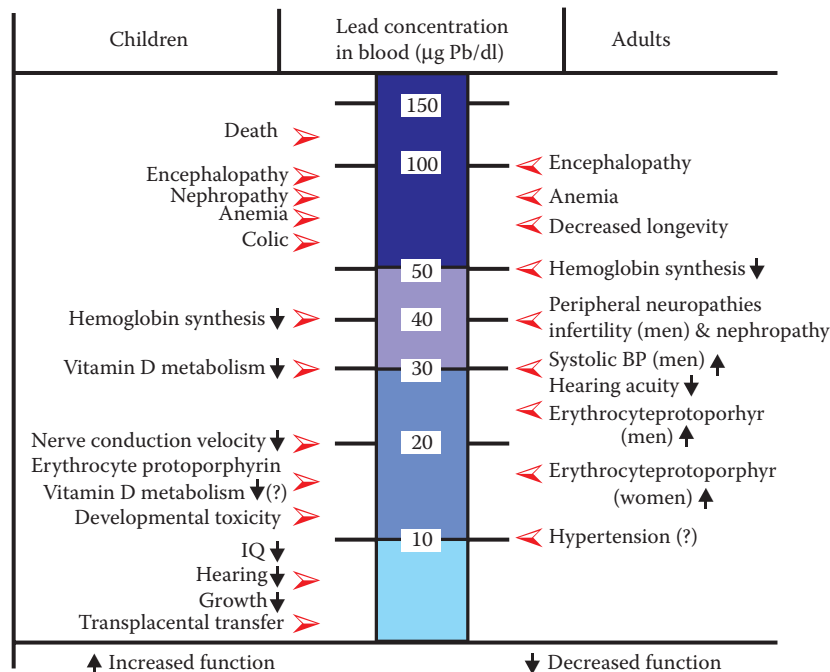


Figure 4.3 Clinical Findings and Blood Lead Levels. A correlation of the clinical findings and rising blood lead levels in children and adults. (Source: U.S. Government Document, Agency for Toxic Substances and Disease Registry.)

Antivenins and Antitoxins

Crotalid Antivenins

Properties

- **Chemistry:** A polyvalent pit viper IgG antivenin prepared in horses hyperimmunized to venoms of the eastern and western diamondback rattlesnakes (*Crotalus* spp.) and the tropical fer-de-lance (*Bothrops* spp.).
- **Mechanism:** Direct Ag/Ab antagonism.
- **Contraindications:** Horse serum allergy, prior antivenin allergy; relative contraindication is a positive skin test. Soon to be replaced by less antigenic polyvalent Crotalid Fab (CroFab®).

Applications

- **Use:** Most rattlesnake envenomations, all Mojave rattlesnake bites, 12% of copperhead and water moccasin (*Agkistrodon* spp.) envenomations.
- **Dose:** At least five (5) vials diluted 1:10 in normal saline IV.
- **Side effects:** Hypersensitivity reactions (20–40%) = urticaria, anaphylactoid reactions, anaphylaxis. Serum sickness (50%) = rash, pruritus, urticaria, arthralgias, lymphadenopathy, rarely immune-complex glomerulonephritis.

Elapid Antivenins

Properties

- **Chemistry:** A polyvalent elapid IgG antivenin prepared in horses hyperimmunized to venoms of eastern and western (Texas) coral snakes, but not to the less venomous Sonoran (Arizona) coral snake.
- **Mechanism:** Direct Ag/Ab antagonism.
- **Contraindications:** Horse serum allergy, prior antivenin reaction.

Applications

- **Use:** All proven eastern and western coral snake bites.
- **Dose:** 3–5 vials, up to 10 vials.
- **Side effects:** Since less antivenin is used for small coral snake envenomations, there are fewer hypersensitivity reactions; nevertheless, serum sickness remains a high possibility.

Centruroides Antivenins

Properties

- **Chemistry:** A specific bivalent (*C. sculpturatus* and *C. gertschi*) hyperimmune IgG prepared in goats at Arizona State University.
- **Mechanism:** Direct Ag/Ab antagonism.
- **Contraindications:** Most adults; reserve for severe envenomations in children.

Applications

- **Use:** Severe (grade III–IV) U.S. scorpion envenomations in children less than age 6.
- **Dose:** 1–2 vials over 30 minutes each.
- **Side effects:** Serum sickness within 2 weeks in 85% of recipients.

Latrodectus Antivenins

Properties

- **Chemistry:** *Latrodectus mactans*-specific IgG prepared in horses.
- **Mechanism:** Direct Ag/Ab antagonism.
- **Contraindications:** Prior allergy.

Applications

- **Use:** Bites of *L. mactans*, *L. hesperus*, *L. bishopi*, and *L. geometricus* that are associated with

severe abdominal pain, myospasm, respiratory insufficiency, and not responsive to intensive therapy.

- **Dose:** 1 vial in 50 mL normal saline.
- **Side effects:** Severe bronchospasm (increased CFR), serum sickness in more than 85% of recipients.

Botulinum Antitoxin

Properties

- **Chemistry:** Trivalent (toxin types A, B, and E) equine IgG antitoxin.
- **Mechanism:** Direct Ag/Ab antagonism.
- **Contraindications:** None; botulism is fatal. Cannot be used to treat infant botulism.

Applications

- **Use:** Foodborne botulism before all toxin is bound and fixed to neuromuscular junction (NMJ) receptors. Infant botulism requires pentavalent (A, B, C, D, E) human hyperimmune globulin.
- **Dose:** One (1) or more vials diluted 1:10 IV every 2–4 hours.
- **Side effects:** Hypersensitivity reactions and anaphylaxis common.

Digoxin-Specific Fab (Antibody Fragment, Antigen-Binding)

Properties

- **Chemistry:** Purified Fab fragments of intact IgG anti-digoxin Abs. No Fc fragments, which do not bind Ag and have increased hypersensitivity reaction potential.
- **Mechanism:** Direct Ag/Ab antagonism of intravascular free digoxin with enough cross-reactivity to also bind digitoxin and the natural cardiac glycosides from garden plants (foxglove and oleander) and amphibians (toad bufotoxins).
- **Contraindications:** Hypercalcemia, concomitant Ca administration — as in CCB overdose.

Applications

- **Use:** Digitalis (digoxin) toxicity = worsening atrioventricular (AV) block, ventricular tachycardia (VT), ventricular fibrillation (VF), rising K greater than 5 mEq/L; natural glycoside poisonings — foxglove, oleander, red squill, toad bufotoxins.
- **Dose:** Empiric 10–20 vials; 38 mg Fab per vial will bind 0.5 mg digoxin.
- **Side effects:** Acute hypokalemia, worsening of congestive heart failure (CHF), rash, potential for hypersensitivity and serum sickness.

Specific Antagonists

Calcium Channel Blocker Antagonist: Calcium

Properties

- **Chemistry:** Ionized cation essential in all muscle and nerve functions, especially for excitation-contraction coupling in heart and peripheral circulation.
- **Mechanism:** Direct antagonist to the cardiac effects of calcium channel blockers (CCBs), K, and Mg and to the neurological effects of Mg; restores Ca in ethylene glycol and hydrofluoric acid (HF) poisoning; complexes with fluoride to limit HF burns.
- **Contraindications:** Digitalis toxicity.

Applications

- **Use:** CCB overdose, hyperkalemia, hypermagnesemia, ethylene glycol poisoning, HF burns. Questionable use in beta-blocker overdose and to relieve myospasms after black widow spider bites.
- **Dose:** 1 g CaCl_2 = 3 g calcium gluconate.
- **Side effects:** Increased calcium = nausea, vomiting, constipation, hypertension, worsening digitalis toxicity, injection site tissue irritation.

Benzodiazepine Antagonist: Flumazenil

Properties

- **Chemistry:** A competitive benzodiazepine (BZ) antagonist with little agonist effect.
- **Mechanism:** Occupies the BZ receptor with high affinity and without causing functional change and displaces the BZ agonist.
- **Contraindications:** In coma cocktails, BZ addiction, seizure disorders; can provoke seizures or arrhythmias in overdoses with tricyclic antidepressants (TCAs), carbamazepine, theophylline, chloroquine, chlorinated HCs, and chloral hydrate.

Applications

- **Use:** To reverse pure BZ overdose or therapeutic BZ use for “conscious sedation.”
- **Dose:** 1–3 mg IV slowly titrated at 0.1 mg/min.
- **Side effects:** Seizure and arrhythmia induction in the predisposed with preexisting seizure disorders, or in overdoses with convulsants; re sedation; rebound BZ respiratory depression.

Opioid Antagonists

Properties

- **Chemistry:** Pure competitive opioid antagonists = naloxone, naltrexone, and nalmefene.
- **Mechanism:** Competitive antagonists most potent at the mu receptor, subserving analgesia, respiratory and CNS depression.
- **Contraindications:** Long-acting naltrexone should not be administered to the potentially opioid-dependent without an initial short-acting naloxone opioid withdrawal test.

Applications

- **Use:** Naloxone to reverse mu receptor effects; questionable use in septic shock. Naltrexone better than nalmefene for treatment of chronic opioid and alcohol addiction.
- **Dose:** 0.4 mg naloxone IV titrated to effect in 0.1-mg increments; long-acting naltrexone 50 mg orally four (4) times a day.
- **Side effects:** Withdrawal in the opioid-dependent, opioid re sedation; rarely noncardiogenic pulmonary edema, hypertension (HTN), and dysrhythmias.

Anticholinesterase (AChE) Antagonist: Physostigmine

Properties

- **Chemistry:** A carbamate (organophosphate insecticide) anticholinesterase (AChE) agent.
- **Mechanism:** Antagonizes cholinesterase (ChE) at both peripheral nervous system (PNS) and CNS sites reversing anticholinergic effects at central sites more than at muscarinic and nicotinic receptor sites by increasing Ach concentrations.
- **Contraindications:** TCA overdose, AV block, bronchospastic disease, peripheral vascular disease (PVD), gastrointestinal or bladder outlet obstruction.

Applications

- **Use:** Peripheral muscarinic (dry mucosa and skin, fever, flushing, mydriasis, tachycardia, urinary retention = *“red as a beet, dry as a bone, hot as Hades”*) and central (agitation, delirium, hallucinations, seizures = *“mad as a hatter”*) anticholinergic toxidrome; more effective reversal of CNS effects than muscarinic and nicotinic effects.
- **Dose:** 1–2 mg IV slowly.
- **Side effects:** Bradycardia, hypersalivation, bronchospasm; rapid administration = nausea, vomiting, headache, and diaphoresis = cholinergic toxidrome = SLUDE = Salivation, Lacrimation, Urination, Defecation, Emesis; or DUMB-BELS = Diarrhea, Urination, Miosis, Bronchorrhea, Bronchospasm, Emesis, Lacrimation, Salivation.

Heparin Antagonist: Protamine

Properties

- **Chemistry:** An electropositively charged protein derivative of salmon sperm.
- **Mechanism:** Complexes with electronegatively charged heparin with a greater affinity for heparin than for antithrombin-III, and dissociates the heparin-AT-III complex in favor of a protamine-heparin complex.
- **Contraindications:** Prior protamine or fish (salmon) allergy, prior vasectomy with sperm autoantibodies, protamine containing insulin preparations (NPH and PZI), sole administration without heparin.

Applications

- **Use:** To reverse heparin activity, usually after cardiopulmonary bypass.
- **Dose:** 1–1.5 times the heparin dose (100 U heparin = 1 mg) based on an activated clotting time (ACT) normal of 150 seconds.
- **Side effects:** Hypotension from vasodilation, anaphylaxis, bleeding from platelet aggregation with quantitative thrombocytopenia.

Vitamins

Folic and Folinic Acids

Properties

- **Chemistry:** An essential water-soluble vitamin, whose active form, folinic acid, is required for DNA (purine and thymidine) synthesis.
- **Mechanism:** Folic acid increases formic acid metabolism and decreases formate levels in methanol (and formaldehyde) poisoning; dihydrofolate reductase (DHFR) converts folic acid to its active form, folinic acid. The cancer chemotherapeutic agent, methotrexate (MTX), inhibits DHFR and blocks folic acid activation to folinic acid.
- **Contraindications:** Use only folinic acid, not folic acid, for MTX overdose.

Applications

- **Use:** Folic and folinic (leucovorin) acids can be used to decrease formate levels in methanol (and formaldehyde) poisoning and reduce risks of oculotoxicity; folinic acid, not folic acid, is the specific antidote for MTX overdose.
- **Dose:** Folic acid, 70 mg, 1–2 mg/kg every 6 hours; leucovorin, 2 times MTX dose in mg as soon as possible and every 6 hours three times a day.
- **Side effects:** None; folic acid is useless for MTX (a DHFR inhibitor) overdose; must use folinic acid, the activated form of folic acid.

Hydroxocobalamin (vitamin B₁₂ precursor)

Properties

- **Chemistry:** A cobalt-containing active vitamin B₁₂ (cyanocobalamin) precursor.
- **Mechanism:** Displaces cyanide (CN) from cytochrome oxidase to form cyanocobalamin, which is an essential vitamin that is either excreted in the urine unchanged and/or detoxi-

fied by the thiosulfate-rhodanase-thiocyanate pathway, especially during CN poisoning.

- **Contraindications:** None.

Applications

- **Use:** Administer along with thiosulfate for cyanide poisoning (not FDA-approved for CN poisoning in the United States).
- **Dose:** 4 g IV, repeat one (1) time, maximum 8 g, co-administer 8 g sodium thiosulfate.
- **Side effects:** Skin reddening, skin allergy.

Vitamin K (vitamin K₁)

Properties

- **Chemistry:** The *ko*agulation factor, an essential fat-soluble vitamin, which exists as two types: (1) the plant vitamin Ks predominantly, phylloquinone but also phytonadione (K₁); and (2) the bacterial vitamin K = menaquinone (K₂), synthesized by gastrointestinal bacteria, except in newborns without an established intestinal flora.
- **Mechanism:** Activate clotting factors II, VII, IX, X.
- **Contraindications:** Allergy to colloidal formulation.

Applications

- **Use:** Warfarin (coumadin)-induced vitamin K_{1,2} deficiency and bleeding, newborn vitamin K₂ deficiency, malabsorption syndromes, and malnourishment.
- **Dose:** 25–50 mg IV or subcutaneously 50–100 mg PO three times a day for 1–2 days.
- **Side effects:** Anaphylactoid reaction from rapid IV administration, hematoma from IM administration.

Pyridoxine (vitamin B₆)

Properties

- **Chemistry:** The stable precursor to active vitamin B₆, a cofactor in the metabolism of neurotransmitters, GABA and 5-HT.
- **Mechanism:** Isoniazid (INH) and monomethylhydrazine (MMH) poisoning — anticonvulsant effects mediated by enhanced GABA activity. Ethylene glycol (EG) poisoning — redirects the metabolism of EG away from the production of its toxic metabolite, oxalic acid.
- **Contraindications:** None; relative contraindication — preexisting peripheral neuropathy.

Applications

- **Use:** (1) INH overdose and MMH poisoning (MMH = gyromitrin from *Gyromitra esculenta* mushrooms, MMH-containing jet fuels); (2) ethylene glycol poisoning.
- **Dose:** INH — mg/mg to maximum 5g; MMH — 25 mg/kg, maximum 70 g/g; EG-100 mg/d to maximum 5g.
- **Side effects:** Acute neurotoxicity = ataxia, incoordination, seizures, all indicate increased case fatality rates (CFR); chronic = delayed sensory peripheral neuropathy — axonopathy, potentially permanent.

Thiamine (vitamin B₁)

Properties

- **Chemistry:** Water-soluble essential B₁ vitamin that maintains the glycolytic pathway, produces ATP for cellular energy, and ensures nerve conduction.
- **Mechanism:** Catalyzes pyruvate metabolism to acetyl CoA, links glycolysis to Krebs's cycle, and promotes ATP generation from cellular energy.
- **Contraindications:** None.

Applications

- **Use:** (1) Alcoholics and ethanol overdoses; (2) coma cocktail for all altered mental status cases to prevent wet beriberi (high output CHF) and dry beriberi (Wernicke's encephalopathy and Korsakoff's psychosis, increased CFR); (3) co-administer with hypertonic dextrose; (4) ethylene glycol (EG) poisoning to promote as a co-factor a less toxic metabolic pathway.
- **Dose:** 100 mg IV or im four (4) times daily.
- **Side effects:** Few; deficiency = wet (CHF) and dry (psychosis) beriberi.

Niacin (nicotinic acid) and Niacinamide (nicotinamide)

Properties

- **Chemistry:** Water-soluble, B-complex vitamin and essential precursor for NAD (and NADP) metabolism that also binds lipoproteins.
- **Mechanism:** Protects hepatic pentose phosphate pathway; provides precursors to pancreatic B-islet cells for NAD (and NADP) production.
- **Contraindications:** Preexisting allergy, ASA sensitivity, skin disorders.

Applications

- **Use:** (1) Niacin in massive doses (10–100 × RDA) to reduce triglyceride and cholesterol levels; (2) niacinamide (nicotinamide) as a specific antidote for Vacor (PNU) rodenticide poisoning to prevent toxic acute Type I insulin-dependent diabetes mellitus (IDDM).
- **Dose:** Niacinamide (nicotinamide) — 500 mg IV stat, then 200 mg IV every 4 hours for 48 hours.
- **Side effects:** Potentially severe prostaglandin (PG)-mediated vasodilation, flushing, headache, nausea, vomiting, diarrhea, niacin hepatitis.

Specific Antidotes

Ethanol

Properties

- **Chemistry:** The highest affinity substrate for the hepatic enzyme alcohol dehydrogenase (ADH), which also metabolizes EG to oxalic acid and methanol to formic acid, highly toxic metabolites of both poison alcohols.
- **Mechanism:** Competitive antagonism of ADH to inhibit toxic alcohol metabolism to oxalic and formic acids.
- **Contraindications:** None.

Applications

- **Use:** To arrest the further metabolism of EG and methanol to their toxic metabolites.
- **Dose:** IV (10%) or orally (20–30%), load 0.8 g/kg IV or 8 mL/kg orally over 20–60 minutes, to maintain a serum level of 100–150 mg/dL.
- **Side effects:** IV-venous irritation and phlebitis, CNS depression, diuresis promotes dehydration with hyponatremia, initial hyperglycemia promotes subsequent hypoglycemia.

Fomepizole (4-methylpyrazole)

Properties

- **Chemistry:** A specific inhibitor of ADH that acts synergistically with ethanol in EG and methanol poisoning to occupy ADH.
- **Mechanism:** 4-MP blocks ADH by complexation.
- **Contraindications:** None.

Applications

- **Use:** Alternative to, or in combination with, ethanol for ethylene glycol, diethylene glycol (“*Haitian Home Tylenol*”), and methanol inges-

tions; and potentially for severe ethanol-disulfiram reactions.

- **Dose:** IV load with 15 mg/kg, then 15 mg/kg every 12 hours.
- **Side effects:** Nausea, headache, dizziness, rash, eosinophilia, elevated liver function tests (LFTs).

n-Acetylcysteine (NAC)

Properties

- **Chemistry:** A thiol (HS)-containing antioxidant and amino acid (cysteine) precursor deacetylated *in vivo* to cysteine that is required for glutathione synthesis.
- **Mechanism:** Replenishes hepatic glutathione (an antioxidant free O⁻ radical scavenger) in acetaminophen overdose and limits the alternate path P450 metabolism of acetaminophen to its toxic metabolite, n-acetyl-*p*-benzoquinonimine (NAPQI).
- **Contraindications:** Do not co-administer with AC (20% adsorbed), separate administrations by 1–2 hours.

Applications

- **Use:** (1) All acetaminophen overdoses, especially in patients with preexisting glutathione depletion (alcoholics — malnourished, HIV-AIDS, P450 inducing drugs); (2) free radical scavenging in poisonings with carbon tetrachloride, chloroform, dichloropropane, and cyclophosphamide.
- **Dose:** “*Rule of 7s*” = administer 140 mg/kg orally within 8 hours, then 70 mg/kg every 4 hours over 3 days for 17 doses in 72 hours.
- **Side effects:** Oral administration (PO) — anticipate vomiting (co-administer an antiemetic), IV administration (not approved) — coagulopathy, anaphylaxis.

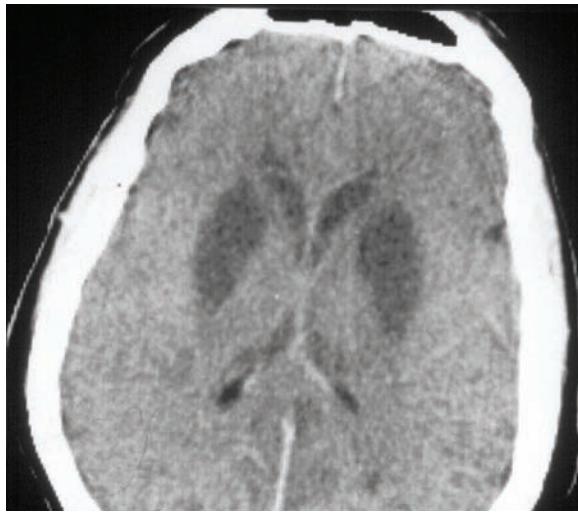


Figure 4.4 X-ray # 40. Cerebral Effects of Carbon Monoxide Poisoning. Cranial computerized axial tomogram (CT) at the level of the basal ganglia in a patient with atypical Parkinson's disease who suffered carbon monoxide poisoning in a house fire that demonstrates bilateral hypodensities in the basal ganglia. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Pralidoxime (2-PAM)

Properties

- **Chemistry:** An oxime nonspecific cholinesterase (both acetyl and pseudocholinesterase) reactivator.
- **Mechanism:** Greater AchE reactivation at central and nicotinic (neuromuscular junction) over muscarinic sites, co-administer with atropine for better antimuscarinic coverage.
- **Contraindications:** Sole use without atropine, relative contraindication — carbamate poisoning — treat with atropine alone as the AchE inhibition will not age and will reverse.

Applications

- **Use:** Organophosphate pesticide and organophosphate nerve gas poisoning; AchE will spontaneously reactivate in carbamate poisoning.
- **Dose:** Administer 1–2 g diluted over 30 minutes within 24–48 hours; repeat every 12 hours for 48 hours.
- **Side effects:** Rare — dizziness, blurred vision, and elevated diastolic blood pressure with rapid IV administration.

Miscellaneous Specific Antidotes

TABLE 4.1 Miscellaneous Specific Antidotes

Drugs or Toxins	Specific Antidotes
Cesium	Prussian blue — potassium ferricyanoferrate (chelator)
Colchicine	Colchicine Fabs
Hydrofluoric acid	Calcium gluconate
Paraquat	Fuller's earth (binder)
Potassium	Sodium polystyrene sulfonate (binder)
Lindane	Cholestyramine (binder)
Lithium	Sodium polystyrene sulfonate (binder)
Methotrexate	Folinic acid (leucovorin)
Nickel	Dithiocarb (diethyldithiocarbamate)
Platinum	Dithiocarb (diethyldithiocarbamate)
Thallium	Prussian blue (chelator)
Uranium	Gallic acid
Warfarin	Vitamin K

Nonspecific Antidotes

Dextrose

Properties

- **Chemistry:** Precursor of glucose, the primary energy source for the brain.
- **Mechanism:** Energy substrate.
- **Contraindications:** Relative contraindications = cerebral ischemia, preemies at risk for intracranial hemorrhage, cardiac insufficiency — congestive heart failure (CHF).

Applications

- **Use:** Empiric administration to all patients with coma or altered mental status.
- **Dose:** D₅₀W, 0.5–1.0 g/kg bolus IV.
- **Side effects:** Phlebitis at IV injection sites; seizures and intracranial hematoma in preemies; potential osmotic fluid overload in cardiac insufficiency.

Glucagon

Properties

- **Chemistry:** Hormone secreted by pancreatic alpha cells in response to hypoglycemia.
- **Mechanism:** Mobilizes glucose fuel stores; suppresses insulin release; provides direct inotropic and chronotropic cardiac stimulation like β -agonists but outside the β receptor; relaxes smooth muscle in lower esophageal sphincter, gastrointestinal tract, and biliary tree — all actions mediated via increased cAMP.
- **Contraindications:** Insulin and oral hypoglycemic-induced hypoglycemia; not to be used in lieu of D₅₀W in the initial therapy of comatose patients.

Applications

- **Use:** To reverse overdoses of beta-blockers and calcium channel blockers; to promote gastrointestinal elimination of ingested button batteries.
- **Dose:** Initial bolus, 50 mcg/kg IV.
- **Side effects:** Not arrhythmogenic, dose-dependent nausea and vomiting, hyperglycemia, hypokalemia, allergic reactions from beef or pork glucagon preparations.

Methylene Blue

Properties

- **Chemistry:** A blue dye initially used as a urinary antiseptic and weak antimalarial agent that is both an Hb oxidizer (high doses) and reducer (therapeutic low doses).
- **Mechanism:** Paradoxically both oxidizes oxyHb to metHb at high doses and reduces metHb back to oxyHb at low doses (therapeutic use) via the NADPH-metHb reductase pathway (requires normal G-6-PD).
- **Contraindications:** Absolute (not variant) G-6-PD deficiency — no NADPH — ineffective for reducing sulfmethemoglobin (H₂S-metHb) in H₂S poisoning.

Applications

- **Use:** To reverse methemoglobin (metHb) production by aniline dyes, sulfonamides, sulfones, nitrates and nitrites, KMnO₄; to reduce cyanmet-hemoglobin (cyanmetHb) in CN poisoning treated with nitrites.
- **Dose:** 1–2 mg/kg IV over 5 minutes.
- **Side effects:** metHb at high doses >5 mg/kg and in G-6-PD deficiency, blue skin-mucosa-urine, vomiting, ECG changes.

Medications causing Methemoglobinemia

- **Nitrites and nitrates:** Amyl and sodium nitrite, nitroglycerin (NTG), nitroprusside, silver nitrate.
- **Local anesthetics:** Prilocaine, lidocaine, benzocaine.
- **Antibiotics:** Antimalarials (chloroquine, primaquine), dapsone, sulfonamides.
- **Miscellaneous:** Pyridium, phenacetin, large doses (>5 mg/kg) of methylene blue.

Toxic Chemical Exposures

- **Nitrites and nitrates:** Butyl and isobutyl nitrite, foods with nitrite or nitrate preservatives (processed meats), nitrophenol, silver nitrate, trinitrotoluene (TNT), well-water nitrates (infants), nitrogen oxide gases.
- **Aniline dyes.**
- **Mothballs:** Naphthalene only.
- **Miscellaneous:** Potassium permanganate.

Cyanide Antidote Kit®

Properties

- **Chemistry:** an FDA-approved cyanide antidote kit composed of (1) amyl nitrite pearls for inhalation, (2) 3% sodium nitrite intravenous solution, and (3) 25% sodium thiosulphate intravenous solution.
- **Mechanism:** To induce methemoglobinemia with (1) and (2) in order to preferentially bind CN forming cyanomethemoglobin and limiting poisoning of cytochrome oxidases; to augment hepatic blood flow with (1) and (2) by promoting vasodilation through nitric oxide forma-

tion; to provide preferred substrate with (3) for rhodanase in the presence of CN to form less toxic thiocyanate for renal excretion.

- **Contraindications:** No absolute contraindications. Relative contraindication = renal failure.

Applications

- **Use:** Complete kit — CN poisoning; IV sodium nitrite alone — hydrogen sulfide (H₂S) poisoning; thiosulfate alone — sodium nitroprusside overdose with CN poisoning.
- **Dose:** (1) Amyl nitrite — for inhalation only; (2) sodium nitrite — 10 mL of the 3% solution IV diluted in 100 mL; (3) sodium thiosulfate — 50 mL of the 25% solution IV.
- **Side effects:** Methemoglobinemia — consider methylene blue, 1 mg/kg IV.

Sodium Bicarbonate

Properties

- **Chemistry:** Nonspecific antidote.
- **Contraindications:** Pulmonary edema, congestive heart failure (CHF), renal failure, preemies at risk of intracranial hemorrhage.

Applications

- **Dose:** 1–2 mEq/kg IV bolus.
- **Side effects:** Metabolic alkalosis, increased HCO₃, hypernatremia, fluid overload, hypokalemia, hyocalcemia.

TABLE 4.2 Mechanisms and Antidote Uses: Sodium Bicarbonate

Mechanisms	Antidote Uses
Overrides cardiac Na channel block by alkalinizing blood	TCAs, cocaine, all quinidine-like antiarrhythmics that block Na channels and increase QRS complex duration
Ionizes weak acids, trapping them in blood before receptor activation	Phenobarbital, ASA, formate
Ionizes weak acids, trapping them in urine and increasing tubular excretion	Phenobarbital, ASA, chlorpropamide, and chlorphenoxyacetic acid pesticides (2,4-D; 2, 4, 5-T)
Buffers metabolic acidosis	Ethylene glycol, methanol
Increases solubility of insoluble drugs methotrexate (MTX)	Methotrexate
Forced alkaline diuresis prevents myoglobin dissociation and reduces risks of acute tubular necrosis (ATN) from rhabdomyolysis	Rhabdomyolysis
Neutralizes inhaled acid gases, especially chlorine and chloramine gas	Chlorine and chloramine gas inhalation-nebulized NaHCO ₃

Hyperbaric Oxygen (HBO) Therapy

Properties

- **Chemistry:** HBO is the inhalation of oxygen at pressures >1 atm.
- **Mechanism:** (1) Elevates hydrostatic pressure and decreases gas volumes (air embolism, “bends”); (2) hastens dissociation of CO and H₂S from Hb; (3) hastens dissociation of CO from cytochrome oxidase; (4) inhibits leukocyte sequestration in brain and reduces risks of cerebral reperfusion injury.
- **Contraindications:** Absolute — tension pneumothorax, bleomycin therapy; relative contraindications — sinus congestion, otosclerosis.

Applications

- **Use:** Air embolism (H₂O₂), decompression sickness, carbon monoxide (CO) poisoning,

carbon monoxide, and cyanide (CN) poisoning, methylene chloride poisoning (hepatically biotransformed to CO), H₂S poisoning, CCL₄ hepatotoxicity (by inhibiting the hepatic microsomal oxidase system that produces toxic metabolites).

- **Dose:** Not applicable, depth and length of “dive.”
- **Side effects:** Otic barotrauma, especially ruptured tympanic membrane, claustrophobia, sinus pain, filled tooth pain.

HBO: CO Poisoning

Head CT of a patient with permanent mental status changes (and later parkinsonism) following CO poisoning. Note characteristic symmetrical lucencies of the globus pallidus bilaterally. Neurotoxicity could have been prevented by early HBO.

Poisonings with Over-the-Counter and Opioid Analgesics and Pharmaceutical Additives

Poisonings with Over-the-Counter and Opioid Analgesics: Outline

Acetaminophen (N-acetyl-para-aminophenol*) (APAP) vs. Acetyl salicylic acid (ASA) aspirin

- Epidemiology
- Toxicology
- Clinical manifestations
- Diagnosis
- Treatment

Nonsteroidal anti-inflammatory drugs (NSAIDs)

- Epidemiology of NSAID overdose
- Classification of NSAIDs
- Mechanisms of NSAID toxicity
- Diagnosis and management of NSAID poisoning
- Specific NSAID adverse effects
- Drug–drug interactions
- Specific NSAID toxicities

Opioids

- Opioid: Ag/Antag
- Opioid toxidrome
- Opioid differential diagnosis
- Clinical effects of opioids
- Special consideration opioids
- Management of opioid overdose

* paracetamol in the United Kingdom.

Acetaminophen (N-acetyl-para-aminophenol) (APAP) vs. Acetyl Salicylic Acid (ASA)

Epidemiology

APAP

- APAP is contained in over 100 over-the-counter (OTC) preparations, and fulminant liver failure from APAP overdose is the second most common cause of liver transplantation in the United States (No. 1 cause = hepatitis C).
- More than 100,000 analgesic overdoses per year, over 200 deaths, 46% due to APAP.
- APAP overdose hospitalizations are greater than all other overdose hospitalizations.
- APAP has replaced ASA as the analgesic-antipyretic of choice, especially for children secondary to safety profile, N-acetylcysteine (NAC) antidote, ASA toxicity, and Reye's Syndrome.
- APAP toxicity risk factors: low hepatic glutathione stores in alcoholics and malnourished; P450 enzyme induction from INH, rifampin, anticonvulsants, and chronic alcohol abuse.

ASA

- There are approximately 18,000 aspirin poisonings per year in the United States.
- ASA causes 26% of all analgesic deaths each year; more than 35 deaths per year.
- ASA and viral illness = Reye's (nausea, vomiting, low glucose, high liver function tests (LFTs), and hepatic encephalopathy).
- Over-the-counter (OTC) drugs contain APAP or ASA; therefore, toxicity screens should include both analgesics: more than 100 OTC drugs contain APAP and more than 200 OTC drugs contain ASA.
- Pepto-Bismal® (bismuth subsalicylate) contains 8.8 mg ASA/mL.
- Increased levels of ASA in ointments, liniments, keratolytics (Compound W®), vaporizer oils = methyl salicylate, 1–2 tsp. lethal in children.

- Methyl salicylate (oil of wintergreen): 530 mg ASA/mL; 8 mL = 13,325 mg ASA tablets. As little as 4 mL of methyl salicylate can be lethal in children.

Toxicology

APAP

- 90% of APAP is hepatically metabolized to harmless glucuronide (60%) and sulfate (30%) metabolites excreted in the urine.
- 5–15% of APAP is oxidized by the cytochrome P450 mixed-function oxidases (MFOs) to potentially hepatotoxic n-acetyl-p-benzoquinoneimine (NAPQI).
- NAPQI is normally immediately detoxified by hepatic glutathione conjugation to nontoxic metabolites.

ASA

- ASA is rapidly absorbed in the stomach over the small intestine, unless absorption is delayed by pylorospasm, hypomotility, gastric outlet obstruction, bezoars, or concretion formation.
- Centrally stimulates the brainstem respiratory center, causing hyperventilation and respiratory alkalosis.
- Blocks the Krebs cycle uncoupling oxidative phosphorylation and reduces ATP production.
- Promotes anaerobic metabolism with ketosis, lactic acidosis, and hypoglycemia.

APAP Overdose

- In overdose, NAPQI production outstrips hepatic ability to detoxify NAPQI by glutathi-

one conjugation. NAPQI covalently binds to and arylates hepatocytes, causing massive centrilobular hepatic necrosis, reversible by n-acetylcysteine (NAC), a glutathione precursor and substitute. NAPQI causes proximal renal tubular necrosis and ARF in 25% of the overdoses.

- Therapeutic plasma concentration: 10–30 mg/L; 4 hours — NAC action level ≥ 150 mg/L; significant plasma toxicity level ≥ 250 mg/L.

ASA Overdose

- Adult overdoses present with mixed respiratory and metabolic acidosis; children present only with metabolic acidosis (>40 mg/dL).
- Unique toxic effects include:
 - Reye's Syndrome
 - Non-cardiogenic pulmonary edema from hypoxia and pulmonary hypertension (HTN)
 - Hypoprothrombinemia and platelet dysfunction
 - Nausea, vomiting, slow GI motility, hemorrhagic gastritis
 - Rhabdomyolysis from hypermetabolism, seizure activity, and increased heat production
 - Tinnitus preceding deafness (>20 – 45 mg/dl)

Clinical Manifestations

Acute APAP Poisoning

- **Phase 1 (up to 24 hours):** Asymptomatic or non-specific symptoms, anorexia, malaise, nausea, vomiting, pallor, diaphoresis.
- **Phase 2 (24–72 hours):** Onset of hepatic injury, right upper quadrant (RUQ) pain, high aspartate aminotransferase (AST), then increased prothrombin time (PT) and alanine aminotransferase (ALT).
- **Phase 3 (72–96 hours):** Hepatic necrosis, coagulopathy, jaundice, encephalopathy, coma, all LFTs high, renal failure (25%), ARDS and pancreatitis possible.
- **Phase 4 (4 days–2 weeks):** Recovery, complete hepatic regeneration in survivors.

Acute ASA Poisoning

- **Early acute:** Nausea, vomiting, fever, diaphoresis, tinnitus, tachypnea.
- **Late acute:** (1) CNS = tinnitus, then deafness, vertigo, high fever, hyperventilation, agitation hyperactivity, seizures, delirium, hallucinations, coma; (2) acid-base = respiratory alkalosis and metabolic acidosis; (3) gastrointestinal distress; (4) coagulopathy; (5) metabolic = hypoglycemia, ketonemia, ketonuria; (5) pulmonary = tachypnea, hyperpnea, non-cardiogenic pulmonary edema (NCPE), cardiopulmonary collapse.

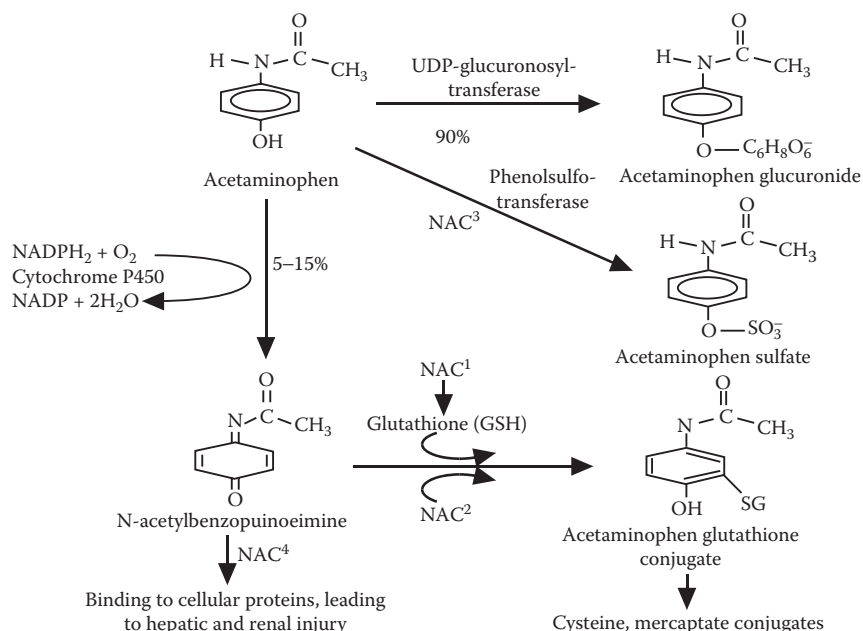


FIGURE 5.1 Acetaminophen (N-acetyl-para-aminophenol-APAP): Biotransformation Pathways of Toxicity. The biotransformation pathways and mechanisms of toxicity of acetaminophen or n-acetyl-para-aminophenol (APAP).

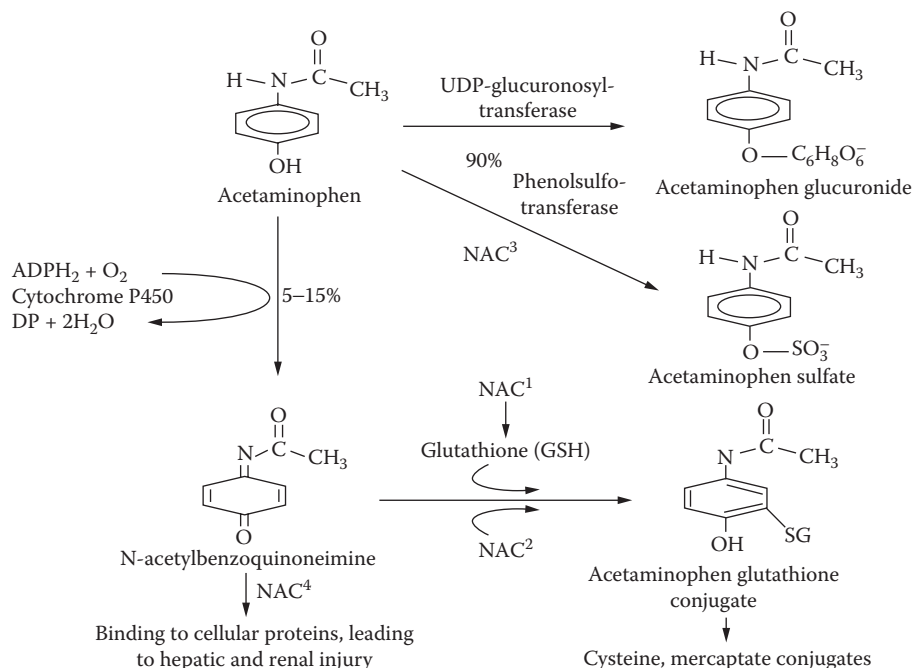


FIGURE 5.2 Acute Acetaminophen (APAP) vs. Aspirin (ASA) Poisoning. The differential mechanisms of poisoning with the common over-the-counter analgesics, acetaminophen and aspirin or acetylsalicylic acid (ASA).

Chronic APAP Poisoning

- **Chronic:** Because APAP is a phenacetin metabolite, renal papillary necrosis and nephrotic syndrome are possible = chronic analgesic nephropathy. In addition, patients at risk of increased NAPQI production as a result of CYP40 enzyme induction (from INH, rifampin, most anti-convulsants, ethanol) or reduced glutathione stores (alcoholism, HIV/AIDS, malnutrition, starvation) are at increased risk of hepatotoxicity from APAP.

- Identify symptoms and signs of hepatic injury: (APAP) plasma concentration 4 hours after overdose (less than 1 hour useless, 2–4 hours OK); hepatic AST if (APAP) above lower nomogram line at 150 mg/mL or RUQ pain; if hepatic AST is 1000+ IU/L, check PT, BUN, and creatinine.
- High risk if: (APAP) above lower nomogram line; (APAP) greater than 150 mg/mL and overdose time unknown-order AST; repeat hepatic AST in 4 hours, for extended release-APAP ingestions.

ASA

Chronic ASA Poisoning

- **Chronic:** (1) Mainly a CNS constellation of tinnitus, deafness, dyspnea, hyperventilation, tachycardia, hyperthermia, CNS hyperactivity, agitation, confusion, slurred speech, hallucinations, seizures, coma; (2) chronic GI distress; (3) NCPE possible.

- Obtain serum ASA: Therapeutic 15–30 mg/dL, toxic when more than 30–40, action level 50 mg/dL, severe toxicity 75 mg/mL, potentially lethal 100 mg/mL.
- Confirm ASA by bedside FeCl₃ test: A few drops (gtts) and 1 mL urine turns purple for a positive test (also positive for acetoacetic acid, diflunisal, phenothiazines, phenylpyruvic acid, phenylbutazone, and phenoxyacetic acid, herbicides).
- Pathognomonic respiratory alkalosis and metabolic acidosis (sole blood gas manifestation in children).
- Confirm positive urine ketones secondary to anaerobic fatty acid metabolism.

Diagnosis

APAP

- Overdose with more than 7.5 g (>20 tablets) in adults, and with more than 150 mg/kg in children.

TABLE 5.1 Acute vs. Chronic ASA Poisoning

	Acute	Chronic
Age	Young	Old
Etiology	Overdose	Iatrogenic
Diagnosis	Classic	Unrecognized
Associated diseases	None	Chronic pain
Suicidal ideation	Yes	No
Clinical	Rapid progression over 30 mg/dL	CNS abnormalities, bleeding tendency, noncardiogenic pulmonary edema possible
Mortality	Rare	25%
Serum levels	High	Intermediate

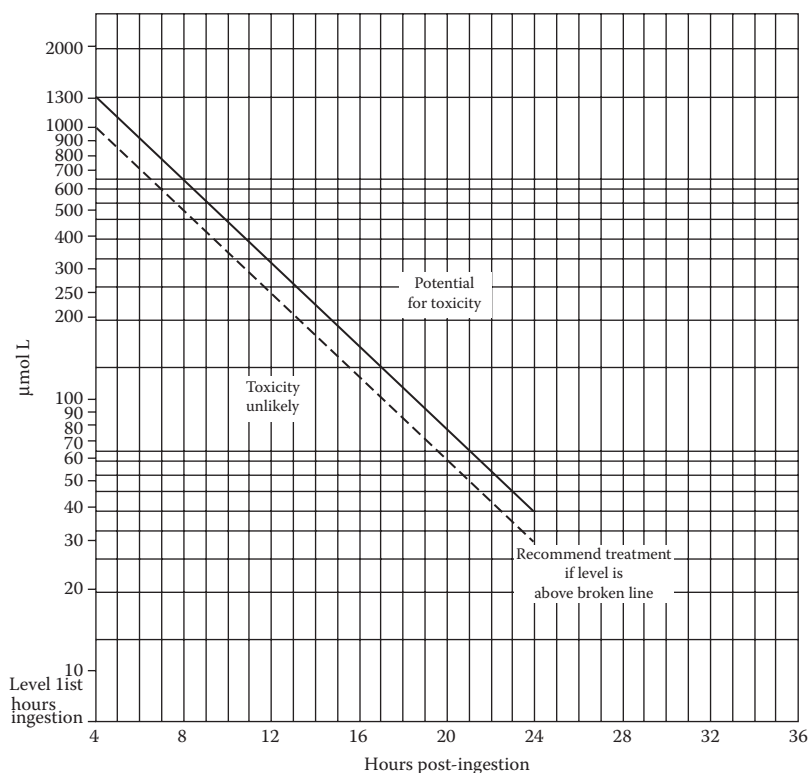


FIGURE 5.3 The acetaminophen (APAP) toxicity nomogram. The acetaminophen toxicity nomogram as determined by amount ingested and time needed for detoxification by nontoxic biotransformation routes. See text for instructions on how to interpret the nomogram.

Treatment

APAP

- Gastric emptying rarely indicated secondary to rapid absorption.
- AC if overdose occurred less than 4 hours ago, separate AC and NAC by 1–2 hours to prevent adsorption of NAC (20%). No AC if ≥ 8 hours post ingestion.
- NAC: Supplies glutathione to detoxify NAPQI, effective up to 8 hours post overdose, possible up to 24 hours post ingestion can even reverse NAPQI binding to hepatocytes.
- NAC oral dosing: Rule of 7s — orally load 140 mg/kg, administer 70 mg/kg every 4 hours \times 17 doses \times 72 hours. Monitor APAP plasma levels every 4 hours.

ASA

- Orogastric lavage and AC.
- Replace fluid, K, Na losses from hypermetabolism and dehydration; monitor CVP or PAP (NCPE risk).
- Alkalinize blood and urine, IV NaHCO_3 (not acetazolamide = metabolic acidosis) for [ASA] over 35 mg/dL, 1–2 mEq/kg bolus and infuse 3 amps/L at 150–200 mL/hour.
- Maintain arterial pH 7.45–7.50 and urine pH 7.5–8.0 (≥ 7.5).
- Support ventilation to maintain respiratory alkalosis; high risk when respiration acidosis and metabolic acidosis present.

n-Acetylcysteine (NAC)

Complications

- Orally: Nausea and vomiting common, add an antiemetic; diarrhea.
- Intravenous: Anaphylactoid reactions and anaphylaxis possible; not FDA-approved in the United States.

Indications for IV NAC

- Uncontrollable vomiting, (1–20%) gastrointestinal bleeding or obstruction, seizure activity, encephalopathy.
- Fulminant hepatic necrosis and liver failure.
- Persistently elevated [APAP] over 8 hours post overdose.
- APAP overdoses during pregnancy.
- Dose: IV load with 140 mg/kg over 1 hour, followed by 1 dose of 70 mg/kg every 4 hours.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Epidemiology of NSAID Overdose

- NSAIDs are now the most commonly prescribed medications, with more than 73 million prescriptions each year and costing \$2.2 billion annually.
- NSAID overdoses cause more morbidity than mortality; CFRs are 6 to 7 times higher for APAP and ASA overdoses than NSAID overdoses.
- Lethal overdoses: ASA > APAP > NSAIDs. CFRs over 10 years: ASA — 0.38%; APAP — 0.12%; NSAIDs — 0.03%
- NSAIDs cause 25% of all reported adverse drug reactions, most commonly gastrointestinal side effects.
- Acute renal failure associated with NSAID use accounts for about 15% of drug-induced renal failure, mostly in the elderly.

Classification of NSAIDs

- **Pyrazolones:** Phenylbutazone only.
- **Fenamates:** The anthranilic acids, meclofenamate and mefenamic acid.
- **Acetic acids:** Diclofenac, etodolac, indomethacin, ketorolac, nabumetone, sulindac, tolmetin.
- **Propionic acids:** Ibuprofen, flurbiprofen, ketoprofen, naproxen.
- **Oxicams:** Piroxicam only (Feldene®).

Mechanisms of NSAID Toxicity

- Most NSAIDs are nonspecific COX-1 and COX-2 inhibitors that block the synthesis of prostaglandins (PGs), which cause inflammation, fever, and pain, especially in osteoarthritis.
- NSAIDs block synthesis of the cytoprotective prostaglandins (PGs), PGE2 and PGI2, which

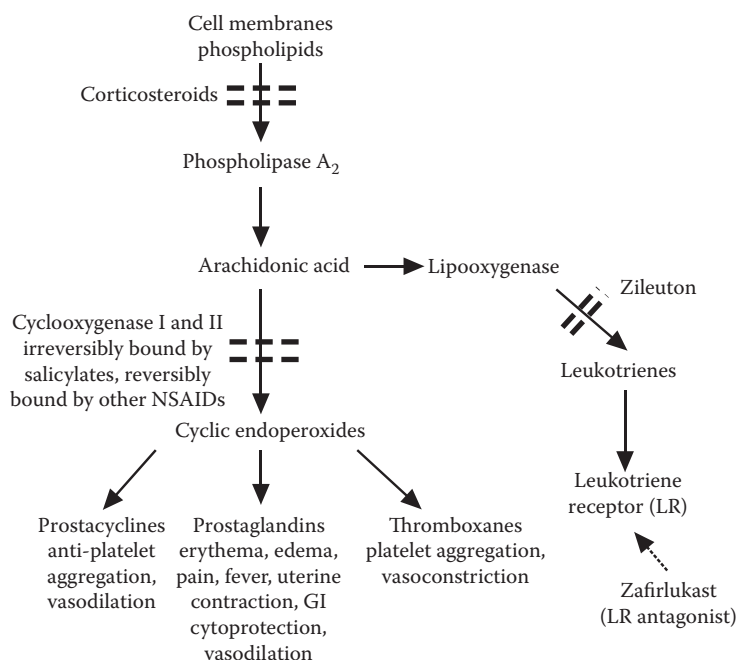


FIGURE 5.4 The Mechanisms of toxicity of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). Comparative toxic biotransformation pathways of common over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs).

maintain upper gastrointestinal mucosal barrier, potentially causing gastric and duodenal ulcers with 3% risk of hemorrhage or gastrointestinal perforation.

- NSAIDs block synthesis of prostacyclins and thromboxanes necessary for normal clotting mechanisms. NSAIDs increase bleeding risks by causing platelet dysfunction.
- NSAIDs are mildly hepatotoxic and cause transient elevations in hepatic transaminases in 25% of patients. Exception: diclofenac (Voltaren®) can cause hepatocellular necrosis, probably via an immunologic or hypersensitivity mechanism.
- NSAIDs are more nephrotoxic than hepatotoxic and can cause chronic renal failure, or analgesic nephropathy, by blocking PG support of renal perfusion and glomerular filtration rate (GFR) with interstitial nephritis, nephrotic syndrome, and papillary necrosis in heavy NSAID abusers, especially elderly women with osteoarthritis.

Diagnosis and Management of NSAID Poisoning

Diagnosis

- **Acute overdose:** CNS depression, respiratory depression, hypotension, hypothermia, gastrointestinal distress, gastrointestinal bleeding, elevated LFTs, acute renal failure, rarely hallucinations and seizures.
- **Chronic overdose:** Chronic renal failure (CRF) in the elderly and alcoholics; bleeding and cognitive dysfunction and dementia in elderly.
- **Constellation of side effects:** Gastrointestinal, renal, hypersensitivity reactions, (acetic acids and phenylbutazone > piroxicam > propionic acid) pulmonary, CNS, hematologic, drug-drug interactions.

Management

- Immediate orogastric lavage and AC, consider MDAC, support.
- Add misoprostol, a PGE2 analog. For gastrointestinal mucosal cytoprotection in chronic NSAID users.
- Switch to specific COX-2 inhibitors (become nonspecific in overdose).
- Hemodialysis useless because of high protein binding.

- Assess for systemic damage: Gastrointestinal, hematologic, hepatic, renal.

Specific NSAID Adverse Effects

Significant Hematologic Side Effects

- Increased bleeding time from decreased platelet aggregation: All NSAIDs.
- Agranulocytosis: Phenylbutazone, naproxen.
- Aplastic anemia: Indomethacin, phenylbutazone, etodolac.
- Hemolytic anemia: Mefenamic acid.
- Neutropenia: Indomethacin.
- Thrombocytopenia: Indomethacin, ibuprofen, naproxen.

Drug-Drug Interactions

- **All anticoagulants and ASA:** High gastrointestinal bleeding.
- **Antihypertensives:** Reduced efficacy of antihypertensives.
- **Sulfonylureas:** Greater hypoglycemic effects.
- **Lithium:** High toxicity.
- **Digoxin:** High toxicity.
- **Aminoglycosides:** High toxicity.

Specific NSAID Toxicities

- **Phenylbutazone:** Most toxic NSAID, seizures, coma, hemodynamic instability, NCPE, ARF, agranulocytosis, aplastic anemia, hypersensitivity hepatitis.
 - Treatment: Immediate orogastric lavage and AC, MDAC, hemodialysis useless.
- **Fenamates (anthranilic acids):** Nausea, vomiting, diarrhea (15%); muscle twitching and seizures.
 - Treatment: Airway and seizure management (BZs), lavage and AC, MDAC.
- **Acetic acids:** Nausea, abdominal cramps, drowsiness, headache, seizures; diclofenac = hypersensitivity hepatitis, hepatocellular necrosis.
 - Treatment: Lavage and AC.
- **Propionic acids:** Gastrointestinal upset, seizure, apnea, coma, ARF, hepatotoxicity, thrombocytopenia.
 - Treatment: Lavage and AC.
- **Oxicams:** Dizziness, blurred vision, coma.
 - Treatment: Lavage and AC.

Opioids

TABLE 5.2 Opioids Receptors

Opioid Receptor	Endogenous Ligand	Clinical Effects
Mu (μ)	Endorphins Naloxone — reversible	Central analog, euphoria, respiratory depression, miosis, dependency, pruritus, cardiovascular depression
Kappa (κ)	Dynorphins Naloxone — reversible	Spinal analog, dyphoria, psychomimesis
Delta (δ)	Enkephelins Naloxone — reversible	Spinal analog, dopamine release modulation
Sigma (σ)	Not a true opioid receptor Not naloxone — reversible	Psychomimesis, seizures (pentazocine)

Opioids: Ag/Antag

- Partial agonist: Buprenorphine.
- Agonists: Codeine, dextromethorphan, diphenoxylate (Lomotil®), fentanyl, heroin, hydrocodone, hydromorphone, loperamide, meperidine, methadone, morphine, oxycodone, paregoric, propoxyphene, tramadol.
- Antagonists: Nalmefene, naloxone, naltrexone.
- Agonist/antagonists: Butorphanol, nalbuphine, pentazocine.
- All α_2 agonists = clonidine (central only) and nasal imidazolines sprays (central and periph agonists, mucosal decongestants).
- Benzodiazepines: Sedation and normal VS, no miosis.
- Phencyclidine (PCP): Despite the miosis, nystagmus is pathognomonic.
- Phenothiazines: Miosis present, severe low blood pressure, dysrhythmias quinidine-like local anesthetic (LA) effect.

Opioid Toxidrome

- Central CNS and respiratory depression.
- Miosis: Mnemonic for miosis = COPS = clonidine (imidazolines), cholinergics, opioids, organophosphates, phenothiazines, phencyclidine, sedative-hypnotics, subarachnoid hemorrhage.
- Gastrointestinal hypomotility and constipation, sphincter spasm, increased intrabiliary pressure, reduced heart rate (HR), not sinus bradycardia.
- Mild hypotension from histamine-mediated vasodilation.

Opioid Differential Diagnosis

- All agonist opioids.



FIGURE 5.5 Opioid toxidrome: miosis, left eye. Pupillary constriction or miosis characteristic of an opioid toxidrome.



FIGURE 5.6 Opioid ileus: heroin addict. Frontal abdominal radiograph (KUB) of a heroin addict consistent with adynamic bowel or opioid ileus that demonstrates diffuse bowel gas distension of the small bowel, ascending colon, and transverse colon. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

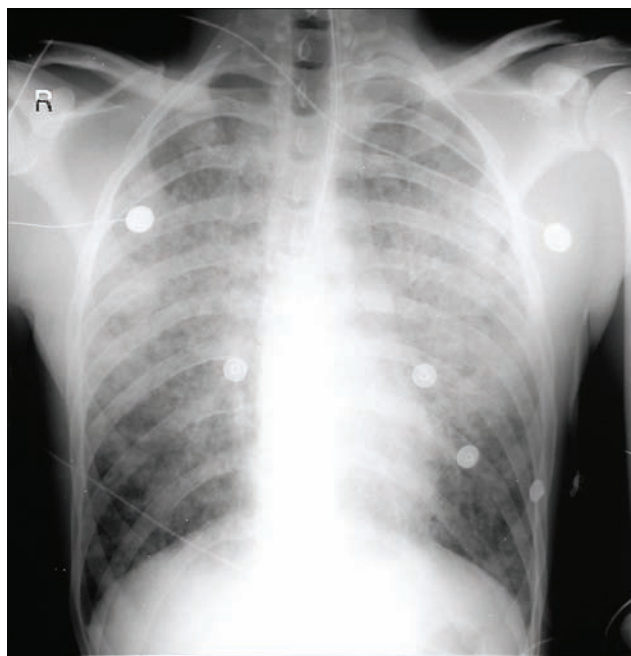


FIGURE 5.7 Noncardiogenic pulmonary edema: aspirin overdose. Frontal chest radiograph of a patient following a suicide attempt by aspirin overdose that demonstrates noncardiogenic pulmonary edema characterized by normal size and configuration of the cardiomeastinal silhouette and diffuse bilateral pulmonary edema. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Clinical Effects of Opioids

- **Respiratory depression:** Low central ventilatory response to both hypoxia and hypercarbia, correlates better with decreased tidal volume more than decreased respiratory rate.
- **Non-cardiogenic pulmonary edema:** Results from a combination of (1) hypoxia stress-induced pulmonary capillary fluid leaks, (2) attempted inspiration against a closed glottis, and (3) naloxone-induced massive sympathetic discharge.
- **Cardiovascular effects:** Venous and arteriolar vasodilation, mild hypotension, and reduced heart rate from histamine release. Note: Propoxyphene induces wide-complex dysrhythmias in a quinidine-like (or local anesthetic-like) effect, responsive to NaHCO_3 .
- **Miosis:** Mechanism of opioid miosis = mu (μ) receptor agonism at the Edinger-Westphal nucleus of cranial nerve III; often inconsistent; meperidine and propoxyphene = normal pupils; but pentazocine (Talwin®), sigma (σ) and kappa (κ) agonists cause dilated pupils. Exceptions:

phencyclidine and all phenothiazines also cause miosis.

- **CNS:** Overdose commonly causes seizures from hypoxia; seizures pathognomonic with meperidine, propoxyphene, and fentanyl overdoses; seizures may occur at therapeutic doses of tramadol (Ultram®).
- **Muscular rigidity:** Acute muscular rigidity with restricted ventilation with rapid IV fentanyl.
- **Nausea and vomiting:** Apomorphine was a classic emetic, a dopamine agonist within the medullary chemoreceptor trigger zone (CTZ). Dopamine antagonists at the CTZ are useful antiemetics = ondansetron.

Special Consideration Opioids

Agonists/Antagonists

- **Mechanism:** Synthetic drugs that are agonist at one opioid receptor, either mu (μ) or kappa (κ),

rarely sigma (σ , pentazocine), and antagonist at another, usually mu (μ); may precipitate acute withdrawal in the opioid-dependent.

- Examples: Butorphanol (Stadol®), nalbuphine (Nubain®), pentazocine (Talwin®, kappa (κ) agonist and mu (μ) antagonist).

Long-Acting Opioids

- **Mechanism:** Synthetic agonists with durations of action of >24 hours; used to provide long-term analgesia for cancer patients, maintenance for addicts, and support during withdrawal; overdose problematic due to short naloxone reversal time (1 hour), resedation, and respiratory depress. Continuous naloxone infusions will be required.
- **Examples (duration of mu agonism):** Methadone and MS-Contin® (24 hours), levo- α -acetyl methadol (LAAM, 3 days).

Meperidine (Demerol®)

- Normeperidine metabolite is neurotoxic, causing tremors, myoclonus, and seizures, especially in renal insufficiency.
- Causes increased presynaptic serotonin release, which can precipitate the serotonin syndrome (hyperthermia, muscle rigidity, and CNS depression), especially when combined with MAOIs or SSRIs. Treatment for serotonin syndrome includes cooling, benzodiazepines, non-depolarizing muscle relaxants.

Propoxyphene (Darvon®)

- Both the parent drug and its norpropoxyphene metabolite have quinidine-like (Class IA) effects and cause QRS widening and dysrhythmias, which are responsive to sodium bicarbonate.
- Overdose may produce acute neurotoxicity from norpropoxyphene metabolite with seizures responsive to benzodiazepines more so than barbiturates.
- Often formulated with APAP, suspect co-toxicities in overdose, and monitor serum [APAP].

Diphenoxylate (Lomotil®)

- Insoluble meperidine analog that delays gastric emptying, coats gut, and immobilizes gastrointestinal tract; used as an antidiarrheal.
- Formulated with atropine for its antimuscarinic effects; overdose may manifest both anticholinergic and opioid toxidromes.
- Long half-life that results from atropine and meperidine analog-induced gastrointestinal immobilization dictates admission for orogastric lavage, AC, and continuous naloxone infusion.

Loperamide (Immodium®)

- An OTC insoluble meperidine analog, like diphenoxylate, that immobilizes gastrointestinal tract; also used as an antidiarrheal.
- Safer than diphenoxylate because loperamide does not contain atropine or delay gastric emptying, does not have a prolonged half-life, and is not associated with prolonged retention of pills in stomach from anticholinergic effects. Overdose management may also require continuous naloxone infusion: (1) wake-up dose = 0.4 mg IV boluses every 2 minutes until arousal; (2) infusion dose = 1/3 of wake-up dose in 1 L of saline (NS) or D5W infused at 100 mL/hour.

Methyl-Phenyl-Tetrahydropyridine (MPTP)

- A neurotoxic byproduct of the illicit lab synthesis of a meperidine analog, MPPP.
- Intravenous drug users (IVDUs) become “frozen addicts” and develop classical parkinsonism from selective destruction of dopamine-secreting substantia nigra cells; resistant to L-dopa treatment.
- MPTP is now used to induce experimental parkinsonism in laboratory animals.

Pentazocine (Talwin®)

- Synthetic agonist/antagonist that is agonist at the kappa (κ) and sigma (σ) receptors (causing dysphoria and psychomimesis), but antagonist at the mu (μ) receptor (producing little respiratory depression).

- Formerly mixed with the blue antihistamine, tripeleminamine = “T’s and Blues,” but now mixed with methylphenidate (Ritalin®) at all-night “Rave” parties.

Tramadol (Ultram®)

- A novel synthetic analog of codeine that is a combined mu opioid agonist and a serotonin/norepinephrine (NE) reuptake inhibitor; only partially antagonized by naloxone.
- Can cause seizures in therapeutic doses and characteristically in overdoses. Seizures respond to benzodiazepine suppression, but may be precipitated by naloxone.
- Can precipitate serotonin syndrome, like selective serotonin reuptake inhibitors (SSRIs), by blocking serotonin reuptake, especially in patients on MAOIs.

Dextromethorphan (Robitussin®)

- An OTC synthetic opioid agonist and analog of codeine with no analgesic activity that is used as a cough suppressant, like codeine.
- In overdose, causes miosis and CNS depression, with choreoathetosis and dystonia from increased presynaptic serotonin release. Also acts as a sigma agonist and can cause a PCP-like psychosis.
- Formulated as a hydrobromide salt = bromism, CNS depression, ataxia, confusion, coma.
- Can also precipitate serotonin syndrome, like meperidine, by increasing presynaptic release of serotonin.

Clonidine (Catapres®)

- Centrally acting alpha₂ agonist that produces an opioid toxidrome (lethargy, miosis, bradycardia, and respiratory depression) indistinguishable from mu agonists due to agonist activity overlap at the mu receptor.
- CNS and respiratory depression reversed by naloxone; always admit for continuous naloxone infusion.
- Used as a sympathetic blocker for hypertension and reflex sympathetic dystrophy, and to provide sympatholysis during opioid withdrawal.

Imidazolines (Afrin®, etc.)

- Combined central and peripheral alpha₂ agonists used as nasal and conjunctival decongestants (oxymetazoline, tetrahydrozoline, xylometazoline) that produce an opioid toxidrome (bradycardia, hypotension, central CNS and respiratory depression) indistinguishable from mu agonists due to agonist activity overlap at the mu receptor.
- Partially naloxone-reversible, but prolonged duration of action (4–8 hours) causes resedation and overdose requires treatment with continuous naloxone infusion.

Heroin Body Packers

- “Mules” who ingest large numbers of multiply wrapped packages of heroin for smuggling, home catharsis, and later street distribution.
- Abdominal x-rays confirm status and direct whole-bowel irrigation (WBI) with polyethylene glycol electrolyte (PEG) in asymptomatic patients.
- Symptomatic heroin packers can be managed medically with AC, naloxone infusion, and WBI (symptomatic cocaine packers need surgery to prevent gastrointestinal ischemic necrosis and high case fatality rates (CFRs)).

Narcotic Adulterants (usually white powders)

Quinine: Disguises bitter taste of heroin, causing dysrhythmias, headache, vertigo, tinnitus, blurred vision, temporary or even permanent blindness.

Scopolamine: CNS and peripheral anticholinergic toxidrome.

Fentanyl analogs: “China white” = fentanyl (100X the potency of MS), sufentanil (10X fentanyl or 1000X MS), and methyl-fentanyl (6000X MS); superpotent fentanyl-adulterated heroin, respiratory arrest, coma, and death. Treatment: CPR, naloxone infusions.

Miscellaneous adulterants: Amphetamines, cocaine, lead-thallium, strychnine, talc.

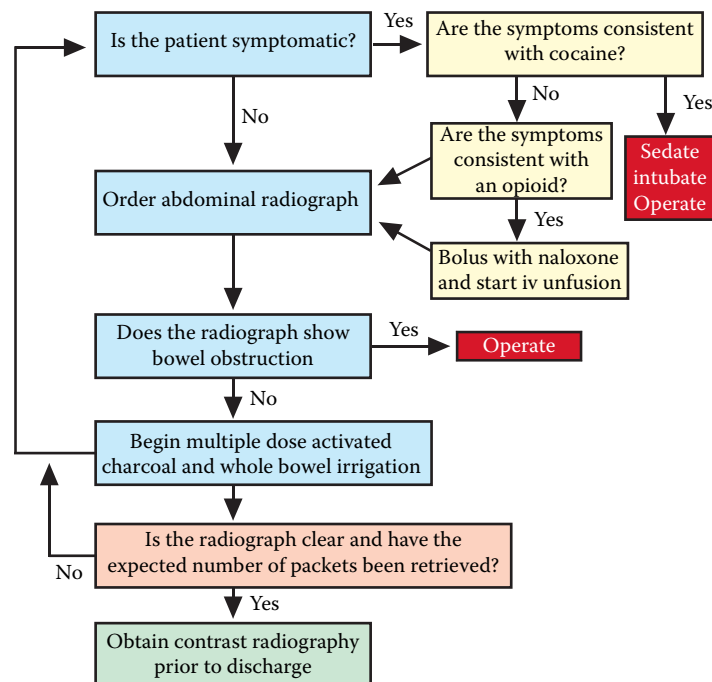


Figure 5.8 Management: cocaine vs. heroin body packers. A flow chart outlining the clinical practice management strategies for body packers of cocaine or heroin.

Management of an Opioid Overdose

Acute Overdose Management

- Low initial IV naloxone boluses (0.1–0.4 mg), rather than a single therapeutic bolus (2 mg) to avoid precipitating acute withdrawal in addicts.
- The aim is to reverse respiratory depression and restore respiratory rate greater than 8.
- Intubate and ventilate if respiratory depression persists, administer 10 mg naloxone IV — no infusion, just prolonged mechanical ventilation.

Naloxone Infusion

- If diagnostic naloxone bolus is successful, administer 2/3 of the initial dose IV per hour.
- If withdrawal develops, stop the infusion to let symptoms abate and restart at 1/2 rate.
- If respiratory depression recurs during infusion, re-administer 1/2 the initial bolus, and increase infusion rate by 1/2.



FIGURE 5.9 Noncardiogenic pulmonary edema: heroin overdose. Frontal chest radiograph that demonstrates normal size and configuration of the cardiomedastinal silhouette with diffuse bilateral non-cardiogenic pulmonary edema following heroin overdose. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Poisonings with Pharmaceutical Additives: Outline

Glycols

- Propylene glycol
- Polyethylene glycol
- Diethylene glycol

Benzyl alcohol

Bromines/Bromides

Chlorobutanol

Thimerosal

Benzalkonium chloride

Phenol

Parabens

Pharmaceutical additive tragedies

- Diethylene glycol-contaminated acetaminophen
- The E-Ferol tragedy
- Eosinophilia-myalgia syndrome

Glycols

Propylene Glycol

Pharmacokinetics and Uses

- **Pharmacokinetics:** Clear, odorless, viscous, volatile alcohol, sweet to taste, and rapidly absorbed; low volume of distribution (V_D), metabolized by alcohol dehydrogenase (ADH) to lactic and pyruvic acids.
- **Uses:** Food and drug preservative, especially parenteral drugs (benzodiazapine [BZs], antidysrhythmics).

Toxicities

- Cardiovascular > metabolic > central nervous system (CNS) > dermal:
 - **Cardiovascular:** Vagomimetic and directly cardiotoxic on rapid IV infusion; bradycardia and hypotension, apnea, wide QRS complex, low T to inverted T waves, elevated ST segment.
 - **Metabolic:** Serum hyperosmolarity, metabolic acidosis (topical silver sulfadiazine in burns).
 - **CNS:** Severe intoxication causes initial CNS depression, then excitation and seizures.
 - **Dermal:** Thrombophlebitis.

Polyethylene Glycol

Pharmacokinetics and Uses

- **Pharmacokinetics:** A family of high-molecular-weight (MW) alcohols also oxidized by ADH to acid metabolites; high MWs limit gastrointestinal absorption — relatively insoluble.
- **Uses:** Bowel preps and whole-bowel irrigation (WBI) solutions (GoLytely®) to cleanse gut; common cosmetic and ointment additives.

Toxicities

- Renal > metabolic toxicities; relatively nontoxic:
 - **Renal:** Potential acute tubular necrosis (ATN) in massive overdose.
 - **Metabolic:** High MW = serum hyperosmolarity, and production of lactic and pyruvic acids = high-anion gap metabolic acidosis, as with propylene glycol.

Diethylene Glycol

Pharmacokinetics and Uses

- **Pharmacokinetics:** An industrial alcohol solvent with a low affinity for ADH with negligible metabolism.
- **Uses:** Industrial solvent, illicitly substituted for propylene glycol as a solvent to solubilize APAP (Tylenol®) manufactured in developing countries (Example: Haiti, Haitian diethylene glycol-contaminated acetaminophen tragedy).

Toxicities

- Initial gastrointestinal and renal > hepatic:
 - **Gastrointestinal:** Initial nausea and vomiting with severe abdominal cramps and pain.
 - **Renal:** Initial polyuria followed within 24 hours by oliguria, then anuria and acute renal failure (ARF). High case fatality rates (CFRs).
 - **Hepatic:** Hepatotoxicity = hepatomegaly and jaundice.
- **Treatment:** Supportive only with hemodialysis (HD); ethanol and 4-methylpyrazole (4-MP) ineffective as antidotes.

Benzyl Alcohol

Pharmacokinetics and Uses

- **Pharmacokinetics:** Colorless aromatic alcohol hepatically oxidized rapidly to benzoic acid, then conjugated with glycine to form hippuric acid; excreted in urine-except in preemies, who cannot conjugate benzoic acid due to hepatic immaturity.
- **Uses:** Common bacteriostatic additive in parenteral medications and IV flush solutions (Gasp-ing-Baby Syndrome).

Toxicities

- Central > Peripheral nervous system toxicities.
- **Gasp-ing-Baby Syndrome:** High benzoic acid levels can cause metabolic acidosis, hypotonia, gasping respirations, seizures, bradycardia, and hypotension with subsequent cardiovascular collapse; high CFRs.
- **Demyelination:** Transient MS-like paraplegia in lower extremities following intrathecal and epidural administration of local anesthetics (LAs) and other drugs (methotrexate) containing benzyl alcohol.

Bromines/Bromides

Pharmacokinetics and Uses

- **Uses:** Emulsifiers and flavor carriers for soft drinks (colas, Ruby Red Squir) and drugs (ipratropium bromide [Atrovent®], dextromethorphan bromide [Robitussin®], pancuronium bromide [Pavulon®]); pesticides (methyl bromide); permanent hair wave solutions.

Toxicities

- Dermal > CNS > gastrointestinal:
 - Dermal: Bromoderma.
 - CNS: Somnolence, sedation.
 - Gastrointestinal: Nausea, vomiting, diarrhea.
- **Antidote:** None.
- **Treatment:** Withdrawal; colchicine to cause microtubular arrest and to reduce neutrophil chemotaxis and release of inflammatory mediators.

Chlorobutanol

Pharmacokinetics and Uses

- **Pharmacokinetics:** An antibacterial-antifungal halogenated hydrocarbon similar chemically to trichloroethanol, the active metabolite of chloral hydrate (“Mickey Finn”).
- **Uses:** Antimicrobial preservative in cosmetics and drugs, especially injectables, otic and ophthalmic topicals (contact lens cleansers).

Toxicities

- CNS > cardiovascular > ocular:
 - **CNS:** Sedative-hypnotic, intoxicating effects, somnolence, then slurred speech, dysarthria, seizures.
 - **Cardiovascular:** Halogenated hydrocarbon that sensitizes the myocardium to catecholamines with PVCs, serious tachyarrhythmias (Vtach, Vfib).
 - **Ocular:** Cytotoxic to corneal epithelium, but less damaging than benzalkonium chloride (BAC).

Thimerosal

Pharmacokinetics and Uses

- **Pharmacokinetics:** An organic mercury compound, formerly Merthiolate®; contains 49% Hg by weight.
- **Uses:** Contact lens disinfectant; vaccine, antivenin, and topical ointment preservative.

Toxicities

- Initial gastrointestinal and CNS > renal:
 - **Gastrointestinal:** Initial severe vomiting, with later hemorrhagic gastroenteritis.
 - **CNS:** Altered mental status (“Mad as a Hatter”), fever, slurred speech, ataxia, later autonomic and ascending sensorimotor peripheral polyneuropathies.

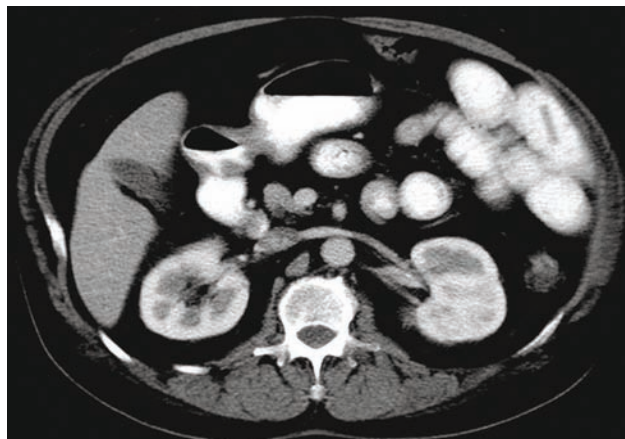


Figure 5.10 Body stuffer: heroin. Axial abdominal oral and intravenous contrast-enhanced computerized tomogram (CT) at the level of the renal veins that demonstrated a rectangular container of heroin in a jejunal loop. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Benzalkonium Chloride

Pharmacokinetics and Uses

- **Pharmacokinetics:** A quaternary ammonium cationic surfactant with immediate antimicrobial activity and delayed cytotoxic activity.
- **Uses:** The most widely used contact lens disinfectant and ophthalmic preservative with immediate onset and long duration of action and tissue penetration; used in most ophthalmic preparations.

Toxicities

- Ocular > ENT mucosal:
 - **Ocular:** Progressive cytolytic degeneration of corneal epithelium with eye pain and photophobia; chronic keratitis.
 - **ENT:** Decreased viscosity of the normal protective mucus blanket, nasal drying, epistaxis.

Phenol

Pharmacokinetics and Uses

- **Pharmacokinetics:** Also known as carbolic acid, the original surgical antiseptic solution and chemical peel agent; rapidly absorbed. Total dose should be limited to less than 50 mg/10 hours.
- **Uses:** Preservative in injectable meds, chemical peels, injectable neurolytic for cancer pain, diluent for lyophilized glucagon powder and other powdered medications.

Toxicities

- **CNS > cardiovascular:**
 - **CNS:** Drowsiness, respiratory depression, peripheral nerve dissolution (painful peripheral nerve regeneration possible, avoid use as a neurolytic for nonmalignant disease).
 - **Cardiovascular:** Dysrhythmias, especially PVCs.

Parabens

Pharmacokinetics and Uses

- **Pharmacokinetics:** Collectively known as para-hydroxybenzoic acids, methylparaben, and propylparaben; often used in synergistic combination as antimicrobials and preservatives.
- **Uses:** The second most common preservatives in cosmetics, next to water.

Toxicities

- Allergy > reproductive > hepatic toxicities:
 - **Allergy:** High incidence of allergic reactions to food, drugs, and cosmetics containing less than 0.1% (1 mg/mL) parabens.
 - **Reproductive:** Significant spermicidal activity, which supports use in vaginal contraceptive creams.
 - **Hepatic:** Displaces bilirubin from albumin binding sites in newborns with hyperbilirubinemia and potentially, kernicterus.

Pharmaceutical Additive Tragedies

Diethylene Glycol-Contaminated Acetaminophen

- **Pharmacokinetics:** The inexpensive, yet highly nephrotoxic industrial solvent, diethylene glycol, was inadvertently substituted for the pharmaceutical grade, non-toxic solvent, propylene glycol, in order to solubilize acetaminophen preparations locally manufactured by drug companies in Bangladesh, Haiti, Nigeria, and South Africa.
- **Syndrome:** The results of the glycol solvent substitution errors were catastrophic and widespread, resulting in several deaths from acute renal failure, mostly in children, in areas with insufficient access to either temporary hemodialysis or renal transplantation.

The E-Ferol Tragedy

- **Pharmacokinetics:** A vitamin E antioxidant preparation was combined with polysorbate emulsifiers to prevent O₂ toxicity in preemies; pharmacologically similar to the multivitamin polysorbate-containing drops and injectable preparations (Poly-Vi-Sol®, Tri-Vi-Sol®). E-Ferol was recalled in the 1980s.
- **Syndrome:** Intralobular cholestasis, hepatomegaly, renal failure, and thrombocytopenia in preemies; 38 deaths.

Eosinophilia-Myalgia Syndrome

- **Pharmacokinetics:** Contaminated L-tryptophan OTC amino acid supplement recommended for insomnia, PMS, and anxiety. Recalled 1989.
- **Syndrome:** Unexplained peripheral eosinophilia with severe muscular pain, mouth ulcers, arthralgias, rashes, peripheral edema, cough, dyspnea, and elevated liver function tests (LFTs) with thousands of cases worldwide, mostly in women; 36 deaths.

Poisonings with Vitamins, Minerals, Herbal Agents, Alternative, and Complementary Agents

Chapter Outline

Descriptive epidemiology of herbal and vitamin poisonings

Pharmacology of herbal and vitamin poisonings

Pharmacology — plant oils

Toxicology of herbal poisonings

Herbal abortifacients
Cardiovascular toxins
Central nervous system (CNS) toxins
Gastrointestinal toxins
Hepatotoxins
Miscellaneous herbal hepatoxins

Toxicology of vitamin poisonings

Vitamin therapy
Potential toxic vitamins
Hypervitaminosis A
Hypervitaminosis E
Hypervitaminosis C
Pyridoxine (Vitamin B₆) neuropathy
Hypervitaminosis D
Niacin toxicity
Eosinophilia-Myalgia Syndrome
Conclusion

Descriptive Epidemiology of Herbal and Vitamin Poisonings

- An herb is a leafy plant without a woody stem, but herbal preparations include all natural, alternative, and traditional remedies. Twenty-five percent of current, proprietary pharmaceuticals come from plant-herb sources.
- As a result of the Dietary Supplement and Health Education Act of 1994, the FDA has no authority over regulating herbal and vitamin products, unless they prove to be toxic.
- 80% of the world's population use herbal products and vitamins daily; most are benign, and offer no health benefit (e.g., vitamin C and Echinacea) or potentially lethal drug interactions (e.g., St. John's wort and SSRIs; garlic, ginkgo, and ginseng, and anticoagulants [ASA, heparin, warfarin]).
- The most common herb and vitamin delivery forms include capsules (50+%), tablets (15+%), teas and drinks (10+%).
- The most common herb supplement types are single herbs (50+%) and combinations (30+%).
- The most popular herb sales in the United States include Echinacea (10%), garlic (10%), goldenseal* (7%), ginseng (6%), Ginkgo (4.5%), and saw palmetto (4.4%). [* Goldenseal is often used illicitly in unsuccessful attempts to disguise urinary marijuana (THC) metabolites.]
- There are no toxicologic databases on herbal and vitamin toxicity in the United States.
- In Hong Kong, herbal medicine toxicity accounts for less than 1% of all acute hospital admissions, and Western medicine toxicity and drug–drug interactions account for 4.4% of all acute hospital admissions.
- Fatalities have resulted from megadoses of the fat-soluble and lipophilic (stored in liver and brain) vitamins A, D, and E; and “therapeutic” (homeopathic) doses of niacin and tryptophan.

Pharmacology of Herbal and Vitamin Poisonings

Pharmacology – Plant Oils

TABLE 6.1 Pharmacology: Plant Oils

Classes	Toxicities	Examples
Volatile oils: evaporate at room temperature	Mucous membrane and CNS irritants	Catnip, garlic, chamomile
Resins: mixtures of oily plant resins	Strong gastrointestinal irritants	Dandelion, elder, black cohosh root
Fixed oils: long-chain fatty acids	Safe emollients and cooking oils	Olive oil, peanut oil, canola oil, safflower oil
Alkaloids = belladonnas, pyrrolizidines	Anticholinergic, hepatic veno-occlusion	Jimson weed, comfrey, goldenseal
Glycosides: anthroquinones	Irritating cathartics	Aloe, senna (Sennakot®)
Saponins	Mucous membrane irritants, steroids, anticoagulants	Licorice, ginseng
Cyanophores	Release cyanide	Prunus pits (apple, apricot, peach, etc.)

Toxicology of Herbal Poisonings

Herbal Abortifacients

- Aloe
- Aristolochia (birthwort)*
- Bitter melon
- Black and blue cohosh root
- Cantharidin (Spanish fly)**
- Compound Q
- Ergots*
- Feverfew
- Juniper
- Motherwort
- Mugwort
- Nutmeg
- Pennyroyal oil (pulegone)*
- Quinine (Ⓢ oxytotic)*
- Rue
- Sage
- Tansey

[*Highly effective abortifacients; ** insect (blister beetle) toxin.]

Abortifacients: Compound Q?

What Is Compound Q?

- Compound Q is an herbal preparation of the Chinese Trichosanthin plant, which can inactivate viral ribosomes and inhibit HIV replication.
- Pharmacology: Poor oral availability and intense diarrhea on oral administration; severe biphasic neurotoxicity on parenteral administration.
- Toxicity: CNS > dermatologic (hypersensitivity and anaphylaxis) > metabolic (hypoglycemia)
 - CNS: (1) Encephalomyelitis in 24–72 hours with fever, delirium, dementia, myalgias, paresis; (2) coma within 1 week.
- Treatment: Immediate ipecac on observed ingestion, lavage and activated charcoal (AC), supportive.

Cardiovascular Toxins

Aconitine Group

- Representative: Monkshood (wolfsbane).
- Toxins: Parasympathomimetic aconitine alkaloids that cause prolonged opening of sodium channels.
- Antidote: None.
- Diagnosis: Salivation, nausea, vomiting, diarrhea, bradycardia, muscle weakness, ventricular tachycardia, ventricular fibrillation, respiratory failure.
- Treatment: Atropine, pacemaker, gastrointestinal decontamination (consider orogastric tube lavage as determined by level of consciousness and airway protective reflexes and administer AC).

Cardiac Glycosides

- Representatives: Foxglove, oleander, red squill, lily-of-the-valley.
- Toxins: Digitalis and digitoxigenin (foxglove, red squill), oleandrin.
- Antidote: DigiBind®.
- Diagnosis: “Dig-toxicity” = nausea, vomiting, diarrhea, abdominal cramps, bradydysrhythmias.
- Treatment: Monitor digoxin levels and ECG, gastrointestinal decontamination (lavage and AC).

Central Nervous System (CNS) Toxins

Absinthe

- Representative: Absinthe (wormwood).
- Latin: *Artemisa absinthium*.
- Toxins: Thujones (artemisins). (1) Similar neurotoxic actions to camphor. (2) Antimalarial effects — used effectively as antimalarials in China and Southeast Asia, even in mefloquine/

doxycycline-resistant *Plasmodium falciparum* malaria.

- Diagnosis: Absinthism — hallucinations, intellectual deterioration, delirium, psychosis, seizures (most celebrated case = Vincent Van Gogh).
- Treatment: Gastrointestinal decontamination (lavage and AC), supportive therapy.

Belladonnas

- Representatives: Jimson weed (thornapple), henbane, mandrake, nightshade.
- Toxins: Atropine-hyoscyamine, scopolamine-hyoscine.
- Antidote: Physostigmine.
- Diagnosis: “Atropine” poisoning = mydriasis, ileus, urinary retention, dry mouth, fever, flushing, tachycardia, agitation, nervousness (“red as a beet, dry as a bone, hot as Hades, mad as a hatter”).
- Treatment: Gastrointestinal decontamination.

Ephedra

- Representative: Ephedra (ma-huang).
- Toxins: Ephedrine, pseudoephedrine.
- Antidote: None.
- Diagnosis: Sympathomimetic effects cause headache, nervousness, anxiety, flushing, vomiting, hypertension, tachycardia, mania and psychosis, seizures; myocardial infarction (MI) and cerebrovascular accident (CVA) possible.
- Treatment: Gastrointestinal decontamination (lavage and AC), supportive therapy.

Nicotine Agents

- Representatives: Betel nut, tobacco, blue cohosh, broom, chestnut, Lobelia.
- Toxins: Arecholine (betel nut), nicotine (tobacco), lobeline (Lobelia).
- Antidote: None.
- Diagnosis: Bronchospasm, chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), oral and lung cancers.
- Treatment: Gastrointestinal decontamination (lavage and AC), supportive therapy.

Nutmeg and Mace

- Representatives: East and West Indian nutmeg tree.
- Latin: *Myristica fragrans*.
- Toxin: Myristicin — hepatically biotransformed to methamphetamine metabolites.
- Antidote: None.
- Diagnosis: Nausea, vomiting, delirium, euphoria, deep sleep with hypothermia (like Ecstasy [MDMA], or 4-methyl-2-dimethoxyamphetamine).
- Treatment: Gastrointestinal decontamination (lavage and AC), supportive therapy.

Gastrointestinal Toxins

Goldenseal

- Representative: Goldenseal is an herb frequently used as an astringent and to reputedly mask the presence of illicit drugs, especially marijuana, on urine screens. Goldenseal is, however, ineffective as an undetected adulterant and is easily detected by GC/MS (= + drug test).
- Latin: *Hydrastis canadensis*.
- Toxin: Hydrastine.
- Antidote: None.
- Diagnosis: Nausea, vomiting, diarrhea, convulsions, paralysis, respiratory failure.
- Treatment: Gastrointestinal decontamination (lavage and AC), supportive therapy.

Pokeweed

- Representatives: Pokeweed, English ivy, yew, horse chestnut.
- Latin: *Phytolacca americana*.
- Toxin: Phytolaccines (pokeweed), enterotoxins = terpene resins.
- Antidote: None.
- Diagnosis: Nausea, vomiting, diarrhea, cramps, hemorrhagic gastritis, weakness; later diplopia, seizures, dysrhythmias, respiratory failure, lymphocytosis.
- Treatment: Gastrointestinal decontamination (lavage and AC), supportive therapy.

Hepatotoxins

TABLE 6.2 Hepatotoxins

Class	Toxins	Diagnosis	Antidote/Treatment
Pennyroyal	Pulegone — CYP450 toxin, glutathione depleter	Minty breath, seizures, external and vaginal bleeding	Gastrointestinal decontamination, N-acetylcysteine (NAC)
Pyrrolizidines = comfrey and coltsfoot	Pyrrolizidine alkaloids	Hepatic veno-occlusion, cirrhosis, liver cancer	Gastrointestinal decontamination, supportive therapy, monitor liver function

Miscellaneous Herbal Hepatotoxins

TABLE 6.3 Miscellaneous Herbal Toxins

Class	Toxins	Diagnosis	Antidote/Treatment
Aristolochia (birthwort-abortionifacient)	Aristolochic acid	Renal fibrosis and renal failure, vaginal bleeding	Supportive therapy, gastrointestinal decontamination
Garlic	Sulfoxides — alliin and allicin and ajoene (ASA-like)	Nausea, vomiting, diarrhea, dermatitis, external bleeding, ASA potentiation	Supportive therapy, gastrointestinal decontamination
Ginseng	Panax acid = Ginseng Abuse Syndrome (GAS)	Hypertension, tachycardia, agitation, insomnia, morning diarrhea	Supportive therapy, gastrointestinal decontamination
Chamomile	Histamine	Cross reactions with Compositae annuals (ragweed, daisy, chrysanthemums)	Antihistamines, bronchodilators

TABLE 6.4 Toxic Herb–Drug Interactions

Herbs	Drugs	Toxicities
Ephedra ^a	Blood pressure drugs	Hypertension, MI, CVA
Feverfew	ASA, anticoagulants	Bleeding
Ginkgo ^a	ASA, anticoagulants	Bleeding
Ginseng ^a	ASA, anticoagulants	Bleeding
Kava	Benzodiazepines (Xanax®)	Delirium
Licorice ^a	Digoxin	Hypertension, CHF
St. John's wort ^a	MAOIs, SSRIs	Depression, suicide, serotonin syndrome
Yohimbe ^a	Antihypertensives	Hypertension, MI, CVA

Note: ASA = Acetyl-salicylic acid (ASA); CVA = cerebrovascular accident; CHF = congestive heart failure; MAOIs = monoamine oxidase inhibitors; MI = myocardial infarction; SSRIs = selective serotonin reuptake inhibitors.

^a Fatal cases reported.

Toxicology of Vitamin Poisonings

Vitamin Therapy

- Vitamins are used therapeutically to manage or prevent several diseases. Example: vitamin A for acne, vitamin C for colds, vitamin E for prostate cancer, vitamin D for osteoporosis, niacin for hypercholesterolemia.
- Vitamins are not usually reported as medications.
- With the exception of folic acid for women of childbearing age, there are no indications for empiric vitamin therapy in developed countries.

Potential Toxic Vitamins

Vitamin A*
Vitamin E*
Vitamin C
Vitamin B₆
Vitamin D* — the most commonly used rat poison in the United States.
Niacin — Nicotinic acid *
Tryptophan (amino acid and serotonin precursor) *

[* Fatalities reported with the fat soluble (A, D, and E) and from niacin-induced anaphylaxis.]

Hypervitaminosis A

Toxicology

- Common name: Vitamin A (deficiency = xerophthalmia).
- Chemical name: Retinol.
- Source: Liver and vegetable carotenoids.
- Recommended Daily Intake (RDI): Females, 25–50 years old, 2700 IU; males slightly higher.
- Toxic dose: 25,000 IU/kg bolus, 25,000 IU per day every 30 days; such doses have been used to treat cystic acne.
- Antidote: None.

Clinical Findings

- Diagnosis: Desquamation and thinning of skin and nails, cheilitis, stomatitis, alopecia, bone changes, cirrhosis, benign intracranial hypertension (BIH) or pseudotumor cerebri = headache, blurred vision, diplopia, optic nerve atrophy, blindness.
- Treatment: Withdrawal, support; spinal taps and diuretics and prednisone for BIH.

Hypervitaminosis E

Toxicology

- Common name: Vitamin E.
- Chemical name: Alpha-tocopherol.
- Source: Meats, grains, and nuts,
- Recommended Daily Intake: Females, 25–50 years old, 15 mg/day; males, 20 mg/day.
- Toxic dose: 400 mg/day.
- Antidote: None.

Clinical Findings

- Diagnosis: Nausea, vomiting, diarrhea, flatulence; vitamin K antagonism can potentiate bleeding induced by heparin, warfarins, and ASA, by further decreasing platelet adhesiveness.
- Treatment: Withdrawal, support therapy.

Hypervitaminosis C

Toxicology

- Common name: Vitamin C (deficiency = scurvy = anemia, gingivitis, petechiae, poor wound healing, bleeding).
- Chemical name: Ascorbic acid.
- Source: Citrus fruits, red fruits, and vegetables.
- Recommended Daily Intake: 60 mg/day.
- Toxic dose: 2 g/day.
- Antidote: None.

Clinical Findings

- Diagnosis: Diarrhea, cystine and calcium oxalate urinary crystals and stones, nephrolithiasis, urosepsis; increased uric acid excretion may mimic acute gout; increased Fe absorption with hemosiderosis, increases sepsis risks from *Vibrio* and *Yersinia*. Nephrolithiasis risks are increased by vitamin D supplementation, as in vitamin D-fortified milk. Vitamin C toxicity can induce oxidative stress with hemolysis in individuals with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency.
- Treatment: Withdrawal, fluid loading, kidney stone lithotripsy.

Pyridoxine (Vitamin B₆) Neuropathy

Toxicology

- Common name: Vitamin B₆.
- Chemical name: Pyridoxine.
- Source: Meats, cereals, vegetables.
- Recommended Daily Intake (adults): 2 mg/day.
- Toxic dose: 150–500 mg bolus, 150–500 mg/day.
- Antidote: None.

Clinical Findings

- Diagnosis: Distal, “glove and stocking” sensory, vibratory, and positional peripheral axonopathy secondary to axonal degeneration; crippling, painful, sensory peripheral neuropathy may be permanent. Other findings include ataxia, dramatic loss of all peripheral sensations (light touch, temperature, vibration, proprioception, pain), and reduced deep tendon reflexes (DTRs).
- Treatment: Withdrawal, supportive.

Hypervitaminosis D

Toxicology

- Common name: Vitamin D (deficiency = rickets = softening and deformation of long bones).
- Chemical name: Cholecalciferol.
- Source: Produced in skin from ultraviolet (UV) light exposed serum cholesterol.

- Recommended Daily Intake: Females, 200 IU/day (5 mcg); males, 400 IU/day (10 mcg).
- Toxic dose: >RDA, increased vitamin D fortified milk, especially in patients overdosing on vitamin C.
- Antidote: None.

Clinical Findings

- Diagnosis: Fatigue, anorexia, nausea, vomiting, diarrhea, hypertension, polydipsia, polyuria, hypercalcemia, cardiac and vascular and ectopic calcifications, hypercalcuria and nephrocalcinosis.
- Treatment: Withdrawal, support, fluids, diuretics, prednisone, calcitonin, biphosphonates.

Niacin Toxicity

Toxicology

- Common name: Niacin, vitamin B₃ (deficiency: pellagra = 3Ds = diarrhea, dermatitis, dementia, stomatitis and glossitis).
- Chemical name: Nicotinic acid — used for high cholesterol reduction.
- Source: Meat, fish, poultry, cereals, nuts, vegetables.
- Recommended Daily Intake (adults): 6–13 mg/day.
- Toxic dose: 60+ mg orally bolus, 60–1000 mg/day.
- Antidote: Preemptive ASA for inhibition of prostaglandin release.

Clinical Findings

- Diagnosis: Prostaglandin-mediated cutaneous flushing and vasodilation, potentiates migraine, pruritus, headache, nausea, vomiting, diarrhea, abdominal cramping, niacin hepatitis with centrilobular cholestasis.
- Treatment: Withdrawal, support, prostaglandin inhibitors (ASA, NSAIDs).

Eosinophilia-Myalgia Syndrome

Toxicology

- Common name: Tryptophan, an amino acid (protein) and serotonin 5-hydroxytryptamine (5-HT) precursor.
- Chemical name: L-Tryptophan.
- Source: All animal proteins.
- Recommended Daily Intake (adults): 30–60 mg/day.
- Toxic dose: 150+ mg/day for more than 2 weeks.
- Antidote: None.

Clinical Findings

- Diagnosis of Eosinophilia-Myalgia Syndrome: Eosinophilia with no indication of parasitic infection or neoplasm (leukemia, eosinophilic granuloma) and generalized myalgias, pulmonary infiltrates, polyarteritis, sclerodermiform skin lesions. Resembles toxic rapeseed oil syndrome (Spain, 1981).

- Treatment: Market withdrawal of recombinant L-tryptophan, formerly used for premenstrual syndrome and insomnia.
- Mechanism of toxicity: Unknown; tryptophan supplements probably contaminated by causative antigenic agents during manufacturing process.

Conclusion

“There cannot be two kinds of medicine — conventional and alternative. There is only medicine that has been adequately tested and medicine that has not.... Alternative treatments should be subjected to scientific testing no less rigorous than required for conventional treatments.”

—M. Angell and J.P. Kassirer
New Engl. J. Med., 339, 1998

Poisonings with Common Household Products

Chapter Outline

Antiseptics

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- Alcohols
- Chlorines
- Oxidants
- Miscellaneous

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- Miscellaneous

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- Osmol gap metabolic acidosis
- Ethanol (EtOH)
- EtOH: Antabuse (disulfiram) reactions
- Isopropanol
- Ethylene glycol (EG)
- Methanol (MeOH)

Toxic deafness and blindness

- Reversible vs. irreversible neurotoxic deafness
- Ototoxicity from aminoglycoside antibiotics
- Neurotoxic blindness

TABLE 7.1 Household Antimicrobials

Antiseptics	Disinfectants	Sterilants
Antimicrobials applied to humans. Example: alcohols, iodophors, chlorhexidine	Antimicrobials applied only to inanimate objects Example: bleach, formaldehyde, phenols	Antimicrobials applied to inanimate objects to kill all microorganisms, including spores
Alcohols	Chlorine bleaches	Example: ethylene oxide, glutaraldehyde
Iodines	Phenols	Ethylene oxide
Chlorines	Boric acid	Glutaraldehyde
Oxidants	Formaldehyde	
Hydrogen peroxide (H ₂ O ₂)		
Potassium permanganate (KMnO ₄)		
Benzalkonium chloride		

TABLE 7.2 Antiseptics: Iodines

Iodine	Iodophor	Iodide
Elemental I ₂	I ₂ + high-molecular-weight nontoxic iodine-carrier (e.g., I ₂ + povidone = Betadine®)	Reduced I ⁻ , multiple uses: 1. SSKI for hyperthyroidism 2. NaI added to table salt 3. X-ray contrast agents
Free I ₂	Relatively safe, mostly skin irritants, commonly used for surgical procedures	Least toxic forms of iodine
2% tincture of iodine		
Most toxic form of iodine, rarely used today		

Antiseptics

Iodines

- Toxicity: Gastrointestinal > dermal > CNS:
 - Gastrointestinal: Caustic hemorrhagic gastroenteritis, necrotic mucosal ulcerations, late esophageal stricture.
 - Dermal: Caustic burns, contact dermatitis (iodophor), ioderma acne (iodide).
 - CNS: Metabolic acidosis, delirium, vasomotor collapse.
- Treatment: No emesis; careful aspiration; lavage with starch, milk, or sodium thiosulfate to reduce most toxic elemental iodine (I_2) to the least toxic iodide (I^-); activated charcoal (AC) and early endoscopy.

Iodides

- Toxicity: Iodism = dermal > airway > gastrointestinal:
 - Dermal: Ioderma acne.
 - Airway: Painful swelling of salivary glands with sialorrhea = acute parotitis = “iodine mumps,” upper airway obstruction.
 - Gastrointestinal: Metallic taste, nausea, vomiting, gingivitis, sialorrhea, no gastrointestinal mucosal burns.
- Treatment: Corticosteroids for parotitis.

Alcohols

Ethanol (70%)

- Chemical name: Ethyl alcohol — least toxic alcohol.
- Toxicity: CNS > pulmonary > dermal:
 - CNS: Intoxication leads to CNS and respiratory depression.
 - Pulmonary: Respiratory depression, aspiration pneumonitis.
 - Dermal: Defatting skin irritant.
- Treatment: Supportive.

Isopropanol (70%)

- Chemical name: Isopropyl alcohol — more toxic than ethanol.
- Toxicity: CNS > pulmonary > gastrointestinal > dermal (defatting skin irritant):
 - CNS: Intoxication, acetone breath, ataxia then CNS depression > ethanol.
 - Pulmonary: Tracheobronchitis, respiratory depression, ketonemia and ketonuria without metabolic acidosis.
 - Metabolic: Exception = only toxic alcohol not causing metabolic acidosis.
 - Gastrointestinal: Nausea, vomiting, crampy abdominal pain, hemorrhagic gastritis.
- Treatment: Orogastric lavage; exception = only alcohol adsorbed by AC; hemodialysis is very effective for all toxic alcohols.

Chlorines

Chlorhexidine

- Brand name: 4% Hibiclens® — least toxic antiseptic.
- Toxicity: Gastrointestinal > dermal > hematologic:
 - Gastrointestinal: Mucosal edema, caustic burns.
 - Dermal: Contact dermatitis.
 - Hematologic: Hemolysis following intravenous (IV) administration.
- Treatment: Endoscopy to assess gastrointestinal mucosa.

Chlorates

- Uses: Na and K chlorates — used as mouthwashes (Chloroseptic®) and toothpastes — more toxic than chlorine.
- Toxicity: Hematologic > renal > gastrointestinal:
 - Hematologic: Methemoglobinemia, hemolytic anemia.

- Renal: Proximal tubular damage, anuria, acute tubular necrosis (ATN).
- Gastrointestinal: Earliest symptoms = nausea, vomiting, diarrhea, crampy abdominal pain.
- Treatment: Lavage, AC, methylene blue, hemodialysis.
- Hematologic: Methemoglobinemia, hemolysis, hemolytic anemia, acute tubular necrosis (ATN), hepatotoxicity, ARDS, cardiovascular collapse.
- CNS: Manganism can cause parkinsonism.
- Treatment: No emesis, endoscopy, methylene blue for methemoglobinemia.

Oxidants

Hydrogen Peroxide (3–30%)

- Actions: Gas emboli-forming toxic caustic.
- Toxicity: Cardiovascular > CNS > gastrointestinal:
 - Cardiovascular = air emboli > gastrointestinal.
 - Cardiovascular: H_2O_2 and tissue catalase activity release O_2 bubbles that may embolize to portal circulation, right ventricular, pulmonary circulation, and brain (CNS).
 - Gastrointestinal: Vomiting, crampy abdominal pain, caustic gastrointestinal burns, erosions and ulcers, gastrointestinal bleeding.
- Treatment: Chest/abdominal x-rays for gas emboli and CVP line aspiration of gas bubbles from right atrium; hyperbaric oxygen, no emesis, early endoscopy to evaluate caustic mucosal burns.

Potassium Permanganate

- Actions: Manganese-containing, violet-colored toxic caustic and oxidizer.
- Toxicity: Gastrointestinal > hematologic > hepatorenal > CNS:
 - Gastrointestinal: Nausea, vomiting, mucosal burns of mouth and esophagus > stomach, gastrointestinal bleeding, perforation and stricture.

Miscellaneous

Benzalkonium Chloride

- Brand Name: Zephiran® = a quaternary ammonium compound = all are caustics.
- Toxicity: Gastrointestinal > CNS > cardiovascular:
 - Gastrointestinal: Caustic burns of mouth, tongue, and esophagus.
 - CNS: Depression.
 - Cardiovascular/miscellaneous: Metabolic acidosis, elevated liver function tests (LFTs), low blood pressure (BP).
- Treatment: Supportive and endoscopy.

Mercurials

- Uses: Obsolete topicals.
- Inorganic: Mercury bichloride and merbromin (Mercurochrome).
- Organic: Thimerosal (49% Hg, merthiolate) still used as a preservative in most hyperimmune globulins, antivenoms, and many attenuated and polysaccharide vaccines.
- Mercury (Hg) poisoning: CNS > gastrointestinal.
- Treatment: Dimethylsuccinic acid (DMSA), oral chelation.



FIGURE 7.1 Over-the-counter mercury bichloride Tablets, c. 1890s. Highly caustic, inorganic mercury compounds were commonly sold worldwide as over-the-counter topical antiseptics (mercuric chloride or mercuric bichloride) and infant teething powders (calomel) well into the twentieth century. Accidental ingestions may result in severe oropharyngeal and esophageal burns, hemorrhagic gastroenteritis, hypovolemic shock, acute tubular necrosis, and esophageal stenosis in survivors. (From the antique pharmaceutical collection of James H. Diaz, M.D., Dr.P.H.)



FIGURE 7.2 Mercurochrome (Merbromin) antiseptic, official Boy Scout first aid kit, 1950s. The organic mercury compounds, mercurochrome (merbromin) and thimerosal (merthiolate), were also commonly sold over-the-counter worldwide as topical antiseptics well into the twentieth century. Thimerosal is still added to vaccines and pooled hyperimmune plasma immunoglobulins and antivenoms as a bacteriostatic and fungicidal preservative. Repeated topical applications or accidental ingestions of the organic mercurials may result in mercuric neurotoxicity with slurred speech, tremor, and chorea. (From the antique pharmaceutical collection of James H. Diaz, M.D., Dr.P.H.)

Disinfectants

Chlorine Bleaches

Chlorine

- Uses: More toxic bleaches.
- Toxicity: Pulmonary > gastrointestinal:
 - Pulmonary: Pulmonary irritants causing severe bronchospasm, pulmonary edema, ARDS.
 - Gastrointestinal: Caustic mucosal burns of esophagus may cause later gastrointestinal strictures.
- Treatment: Supportive and endoscopy, later esophageal dilations.

Sodium Hypochlorite

- Chemical and brand names: NaOCl, Clorox®
 - less toxic bleaches.
- Toxicity: Gastrointestinal > pulmonary:
 - Gastrointestinal: Gastrointestinal irritant, mucosal burns, rarely strictures.
 - Pulmonary: Two highly toxic gases can be produced in households by mixing household bleach (NaOCl) and acid (HCl) toilet bowl cleansers, including (1) chlorine gas and (2) chloramine gas.
- Treatment: Supportive and endoscopy.

Phenols

Free, Nonsubstituted Phenol

- Uses of phenol (carbolic acid): Nail bed cauterizer, chemical peeler, neurolytic.
- Brand example: Camphophenique® (camphor and phenol).
- Toxicity (very toxic): CNS > gastrointestinal > dermal:
 - CNS: Stimulation with seizures.
 - Gastrointestinal: Sweet-smelling breath, nausea, vomiting, crampy abdominal pain, bloody diarrhea; rarely mucosal acid burns and esophageal strictures.

- Dermal: Skin burns with later peeling and light brown staining.
- Miscellaneous: Brownish-black urine.
- Treatment: Skin wash with polyethylene glycol (PEG), careful lavage, endoscopy.

Substituted Phenol (Phenol + Halogen)

- Uses: Obsolete hospital skin cleanser.
- Brand example: Hexachlorophene (pHisoHex®).
- Toxicity (less toxic): CNS > gastrointestinal > dermal.
 - CNS: Premies = vacuolar encephalopathy = drowsiness and later cerebral edema.
 - Gastrointestinal: Nausea, vomiting, diarrhea, sore mouth and throat, crampy abdominal pain with fever.
- Treatment: Supportive.

Miscellaneous

Boric Acid

- Uses: Soaps/detergents, contact lens solutions, roach tablets.
- Toxicity (very toxic): Gastrointestinal > dermal > CNS > renal:
 - Gastrointestinal: Greenish-blue vomitus and diarrhea.
 - Dermal: “Boiled lobster” erythroderma with desquamation in 1–2 days, and later patchy alopecia (adults).
 - CNS (children): Lethargy, delirium, seizures, coma.
 - Renal: Low blood pressure, shock-induced acute tubular necrosis (ATN).
- Treatment: No AC, lavage, hemodialysis.

Formaldehyde

- Uses: Tissue fixative, used as a pesticide and fungicide in insulation.

- Toxicity: Gastrointestinal > CNS > pulmonary > dermal/miscellaneous.
 - Gastrointestinal: Nausea, vomiting, diarrhea, caustic hemorrhagic gastroenteritis, stomach > small intestine, mucosal necrosis, gastric perforation, stricture formation metabolism to formic acid with metabolic acidosis.
 - CNS: Initial depression with subsequent coma.
- Pulmonary: Upper airway irritation with bronchospasm, acute pneumonitis possible; association with nasopharyngeal carcinoma unproven.
- Dermal/miscellaneous: Rash and hepatotoxicity.
- Treatment: Lavage, NaHCO_3 , folic acid as a cofactor to promote formate metabolism, endoscopy to assess mucosal injury.

Hospital Sterilants

Ethylene Oxide

- Uses: Hot, dry gas sterilization.
- Toxicity (more toxic than formaldehyde): Potent mucosal irritant; mutagen and carcinogen.
 - Acute: Upper airway, conjunctival, gastrointestinal, and dermal irritation with nausea.
 - CNS: Malaise, light headedness, syncope, seizures, coma, sensory and motor neuropathies, rarely parkinsonism.
 - Chronic: High spontaneous abortion rates, increased rates of leukemias and gastric cancers.
- Treatment: Removal and supportive therapy.

Glutaraldehyde

- Uses: Cold liquid sterilization of endoscopic and other non-autoclavable, heat-sensitive hospital instruments.
- Brand name: Cidex®.
- Toxicity (least toxic hospital sterilant): Predominantly a skin and mucosal irritant.
 - Acute: Increased upper airway reactivity, coryza, epistaxis, occupational asthma, ocular inflammation, conjunctivitis.
 - Dermal: Contact dermatitis.
- Treatment: Removal and supportive therapy.

TABLE 7.3 Mothballs

Camphor	Naphthalene	Para-dichlorobenzene
High toxicity	Moderate toxicity	Low toxicity
Not radiopaque	Faintly radiopaque	Densely radiopaque
Wet and oily	White and dry	White and oily
Float in tap and saltwater	Sink in tap, float in saltwater	Sink in both tap and saltwater
Treatment: sedation, AC, non-oil cathartic = increased absorption	Treatment: AC, non-oil cathartic, methemoglobinemia possible, may require methylene blue therapy	Treatment: not indicated, the safest mothball, most commonly used mothball today in U.S.
Acute toxicity: CNS > gastrointestinal; excitement, tremor, restlessness, seizures, apnea, coma, camphor-smelling breath, initial nausea, vomiting, cramps	Acute toxicity: hematologic > gastrointestinal > CNS; #1 hemolysis, methemoglobinemia possible, hemolysis in G-6-P deficiency, cyanosis, anemia, fever, nausea, vomiting, diarrhea, cramps	Acute toxicity: gastrointestinal > hematologic; mucosal irritant, rarely causes hemolysis and jaundice
Chronic: mimics Reye's syndrome–hepatic encephalopathy	Chronic: aplastic anemia, jaundice, hepatic necrosis	Chronic: rarely causes hepatic necrosis

Hydrocarbons

Hydrocarbon Classification

Mostly Petroleum Distillates

- Acetone and toluene — aromatic
- Gasoline, benzene, kerosene — aromatic
- Butane and propane — aliphatic
- Carbon tetrachloride (CCl_4) — halogenated
- Methylene chloride — halogenated
- Trichloroethane — halogenated
- Trichloroethylene (TCE) — halogenated
- Tetra(per)chloroethylene (PCE, PERC) — halogenated
- n-Hexane and n-heptane — aliphatic
- Methyl-isobutyl ketone (MIBK) — aliphatic

Few Wood (Pine) Distillates

- Pine oil
- Turpentine

Hydrocarbon Uses

- Adhesives and cements
- Fuels and propellants
- Paints and coatings
- Lacquers and varnishes
- Lubricants and oils
- Polishes and waxes
- Paint removers and strippers
- Paint thinners
- Solvents and degreasers
- Spot removers and dry cleaners
- Typewriter correction fluids (Liquid Paper®)

Hydrocarbon Epidemiology

- There are 65,000 hydrocarbon (HC) exposures per year; 95% are unintentional; 60% involve children; 90% of deaths are in children under age 5 years; 50% demonstrate minimal toxic effects; and 20% require treatment.

- There are 20 deaths per year from HC poisoning; 90% of these deaths occur in children under age 5 years; 33% of these deaths involve gasoline/motor oils; 11% involve Freon® and other spray can propellants (usually in adolescent HC inhalation abusers), and 57% involve kerosene.

Hydrocarbon Toxicology

- Toxicities: Pulmonary (50%) > gastrointestinal (5%) > CNS (3%) > cardiovascular > dermal > hematologic.
 - Pulmonary: Pulmonary toxicity predominates and results from HC aspiration and not with HC absorption, with a resulting loss of the surfactant's capability to maintain alveolar surface tension and subsequent ARDS. HC pulmonary toxicity is determined by HC physical properties (i.e., low surface tension, low viscosity, high volatility). These physical characteristics of hydrocarbons will greatly increase aspiration risk with resulting pulmonary toxicity.
 - Symptoms: Gagging, coughing, choking leading to aspiration with bronchospasm, rales, rhonchi, tachypnea, hypoxia; later hemorrhagic pulmonary edema, methemoglobinemia (nitrates, nitrites) with cyanosis; chronic URIs (upper respiratory infections), bronchiectasis, pulmonary fibrosis.
 - X-ray: Pneumonitis, infiltrates, consolidating pneumonias, pleural effusions, barotrauma, upright gastric “double-bubble” sign = (1) air-HC + (2) HC-gastric fluid interfaces.
 - Gastrointestinal (5%): Nausea, vomiting, hematemesis, gastrointestinal mucosal ulcerations.
 - CNS (3%): Seizures, then coma from hypoxia and inhalation of volatile HC — “anesthetics” with progression from Stage II (excitement) to Stage IV anesthesia (coma).
 - Cardiovascular: Myocardial sensitization caused by halogenated hydrocarbons precip-

itates tachydysrhythmias, PVCs, ventricular tachycardia, ventricular fibrillation.

- Dermal: Defatting dry dermatitis, oil boils, degreaser's flush (especially with trichloroethylene) = facial flushing on consumption of ethanol following trichloroethylene exposure.
- Hematologic: Methemoglobinemia, hemolysis, anemia, disseminated intravascular coagulation (DIC).
- Renal: Toluene can cause type I renal tubular acidosis (RTA) with defective tubular acidification manifesting as metabolic acidosis, hyperchloremia, normal anion gap, and very alkaline (high pH) urine.

Treatment of HC Ingestion

- Careful gastrointestinal decontamination: No emesis! No activated charcoal! Possibly gastric lavage with small nasogastric (NG) for large volumes, intentional ingestions, and highly toxic HCs, including (CHAMP) = camphor, halogenated HCs, aromatic HCs, HCs associated with metals, HCs associated with pesticides.
- No cathartics, especially no olive or mineral oil cathartics (oily cathartics will increase absorption of lipophilic HCs), no prophylactic antibiotics or corticosteroids.
- Mechanical ventilation for ARDS: Barotrauma risk = start with low positive end expiratory pressure (PEEP) → next consider, high frequency jet ventilation (HFJV) → for refractory hypoxia, consider extracorporeal membrane oxygenation (ECMO).
- Cardiovascular: Consider avoiding inotropic support during PEEP, due to myocardial sensitization to sympathetic catecholamines and potential arrhythmogenesis.

Volatile HC Substance Abuse

- Techniques: "Sniffing," "huffing," "bagging."
- Agents: Toluene (glues, paints), fuels (butane, gasoline), trichloroethane and trichloroethylene (TCE, typewriter correction fluids, Liquid Paper®), perchloroethylene (PCE or PERC), all dry cleaning fluids (acetone, CCl₄, TCE, PCE).
- Acute toxicity: CNS-excitation = euphoria, hallucinations, ataxia, seizures, headache, then

CNS and respiratory depression > cardiovascular = tachyarrhythmias often resulting in "sudden sniffing deaths" > hematologic = methemoglobinemia > hepatotoxicity (CCl₄ can cause centrilobular hepatic necrosis) and CO poisoning (methylene chloride).

- Acute toxicity: Toluene — renal tubular acidosis.
- Chronic toxicity: "Glue-sniffers" encephalopathy and chronic "painter's syndrome" — both are characterized by memory and cognitive losses, dementia, insomnia, anxiety and depression, personality disorder, ataxia and chorea, peripheral neuropathy (especially n-hexane and methyl-isobutylketone [MIBK]).

Wood Distillates

Pine Oil

- Brand name: PineSol®.
- Pine terpenes.
- Toxicity: Pulmonary > CNS:
 - Pulmonary: Aspiration pneumonitis.
 - CNS: Excitation with hyperactivity (possibly seizures), followed by depression (possibly coma).
- Treatment: Same as for the petroleum distillates.

Turpentine

- Pine terpenes
- Toxicity: Pulmonary > renal > hematologic > CNS:
 - Pulmonary: Aspiration pneumonitis.
 - Renal: Pathognomonic hemorrhagic cystitis, possibly acute tubular necrosis (ATN).
 - Hematologic: Pathognomonic of turpentine = TP thrombocytopenic purpura.
 - CNS: Excitation followed by depression.
- Treatment: Same as for petroleum distillates.
- Unique toxicities: (1) Hemorrhagic cystitis, (2) thrombocytopenic purpura.

Caustics

Acids

- Caustic: Quickly neutralizes to tissue pH.
- Acute: Thermal energy leads to caustic acid burns.
- Chemistry: Acid proton donor.
- Toxic pH: <3.0.
- Chronic: Coagulation necrosis (denaturation of proteins and dessication of fats) causes superficial, split-thickness burns on skin and gastric mucosa; squamous epithelium of the oropharynx and esophagus offers greater protection from acid burns than columnar epithelium of stomach.
- Examples: Battery acid contains H_2SO_4 and toilet bowl cleaners contain HCl.

Alkalis

- Caustic: Quickly neutralizes to tissue pH.
- Acute: Thermal energy leads to caustic alkali burns.
- Chemistry: Alkali proton acceptor.
- Toxic pH: >11.0.
- Chronic: Liquefaction necrosis (solubilization of proteins and saponification of fats) with resulting deep, full-thickness burns of skin and oral and esophageal mucosa; later esophageal strictures possible. The stomach is involved with mucosal burns only 20% of the time following the intentional oral ingestion of alkalis.
- Examples: Drain openers (NaOH) and oven cleaners (NH_4OH).

TABLE 7.4 Sources and Uses of Acids

Acid Source	Acid Uses
Boric acid	Roach tablets
Formaldehyde metabolite (formic acid)	Tissue fixative, pesticide/fungicide effects in foam insulation
Hydrochloric (muriatic) acid	Toilet, brick, and tile cleaners
Hydrofluoric acid	Antirust products
Oxalic acid	Bleaches and whiteners
Selenious acid	Gun bluing agents
Sulfuric acid	Automotive batteries

TABLE 7.5 Sources and Uses of Alkalis

Alkali Sources	Alkali Uses
Ammonium hydroxide (ammonia)	Glass, oven, and other hard surface cleaners (Windex®)
Potassium permanganate	Antiseptics, mouthwashes
Sodium hydroxide	Detergents
Sodium borates, carbonates, phosphates, and silicates	Detergents, dishwasher/scouring powders, water softeners
Sodium hypochlorite (Clorox®)	Bleaches, whiteners, tile surface cleansers, and disinfectants

Pathophysiology

Acid Ingestions

- Immediate tissue burn
- Epithelial coagulation necrosis
- Epithelial penetration limited by coagulation effects
- Systemic metabolic acidosis
- Rarely, orogastric burns and, frequently, esophageal “skip areas”
- Less gastrointestinal ulceration than alkali ingestion
- Few late esophageal strictures
- Collateral acid-induced damage to spleen, pancreas, and biliary tree

Alkali Ingestions

- Immediate tissue burns
- Epithelial liquefaction necrosis
- Deep, full-thickness epithelial penetration
- Tissue necrosis promotes lactic acidosis
- Oropharyngeal, esophageal, and gastric mucosal burns
- More gastrointestinal ulceration than acid ingestions
- Late esophageal strictures are common
- No extraintestinal damage

Symptoms and Diagnosis

Acids

- Symptoms: Oropharyngeal burns, crampy abdominal pain, stridor, pleural effusions suggest gastrointestinal perforation.
- X-ray: Assess for gastrointestinal perforation = pleural effusion, free air, pneumomediastinum, pneumoperitoneum; contrast extravasation suggests perforation with fistula formation.
- Lab: Metabolic acidosis.

Alkalis

- Symptoms: More oropharyngeal burns, greater gastrointestinal perforation and esophageal stricture risks; otherwise similar to acid ingestions.
- X-ray: Perforation more likely; assess for free air, pleural effusions, pneumomediastinum, and pneumoperitoneum; x-ray contrast extravasation suggests gastrointestinal fistula.
- Lab: Lactic acidosis follows massive tissue liquefaction necrosis.

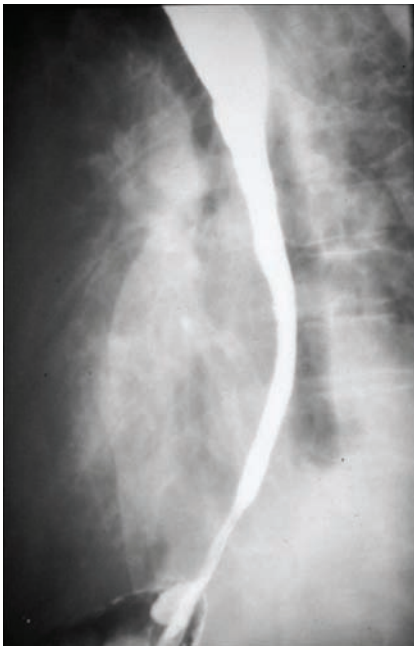


FIGURE 7.3 Esophageal stenosis following lye ingestion. Frontal esophagogram of an adolescent eight months following intentional lye ingestion in a suicide attempt that demonstrates a gradual funnel-like tapering of the distal esophagus and concentric esophageal stenosis. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Same Management

Acids

- Immediate upper airway inspection for extent of mucosal burns.
- Vomiting (ipecac) contraindicated — could result in greater epithelial damage.
- Activated charcoal (AC) contraindicated due to limited absorption and endoscopy interference.
- Immediate dilution therapy with milk > water — both of limited usefulness.
- X-ray assess for gastrointestinal perforation and pleural effusions.
- Perform endoscopy within 12 hours — perforation risk increases 2–3 days to 2 weeks post ingestion.
- No prophylactic antibiotics or corticosteroids.
- Surgical repair, stricture dilation.

Alkalis

- Immediate upper airway inspection for extent of mucosal burns.
- Vomiting (ipecac) contraindicated — could result in greater epithelial damage.
- AC contraindicated due to limited absorption and endoscopy interference.
- Immediate dilution therapy with milk > water — both of limited usefulness.
- X-ray assess for gastrointestinal perforation and pleural effusions.
- Perform endoscopy within 12 hours — perforation risk increases 2–3 days to 2 weeks post ingestion.
- No prophylactic antibiotics or corticosteroids.
- Surgical repair, stricture dilation.

Special Caustics

Special Acids

- Phenol: Dermal and mucosal burns; early endoscopy indicated.

- Hydrofluoric acid: Free F⁻ ions rapidly and deeply bind to Ca and Mg cations, causing painful, subcutaneous tissue burn injuries with few external dermal manifestations — elevated serum K, reduced serum Ca and Mg; subsequent arrhythmias; assess electrolytes immediately. Treatment: Ca gluconate > CaCl₂; Ca gluconate may be administered as topical gel, intradermally, intra-arterially, no Ca gluconate in eyes, Mg citrate orally.

Special Alkalis

- CliniTest® glucosuria tablets: Large CuSO₄ and NaOH tabs can lodge in esophagus, causing severe localized strictures.
- Ammonia: 3–10% home-use concentrations can cause esophageal burns; 28+% can cause severe burns and later esophageal strictures.
- Bleach: Limited burns and no late esophageal strictures.
- Sodium azide: Airbag inflator explosive and lab reagent; mimics CN poisoning, causing cytotoxic hypoxia.

Sodium Azide

- Uses: Airbag releasing agent, common clinical lab reagent for autoanalyzed samples.
- Toxicity: Uncouples oxidative phosphorylation within mitochondria, like CN, by inhibiting cytochrome oxidase, causing cytotoxic hypoxia and metabolic acidosis, and, possibly, producing CN.
- Clinical Poisoning: CNS, cardiovascular, and eye > initial gastrointestinal (nausea, vomiting, diarrhea).
 - Cardiovascular: Vasodilation = hypotension.
 - CNS: Biphasic-initial headache and seizures, then hyporeflexia and coma.
 - Eye: Deeply penetrating liquefaction necrosis.
- EMS personnel risks: On ingestion, combines with gastric HCl to liberate hydrazoic acid and pose toxic risks to all attending medical personnel.

- Treatment: Supportive, ICU monitoring, copious eye irrigation to pH 7.4 (normal saline (NS) > Ringer's lactate (RL) > tap water). Warn EMS personnel of their risks and recommend adequate ventilation and personal protective equipment.

Nail and Hair Care

Artificial Nails

- N,N-dimethy-p-toluidine: Methemoglobinemia.
- Aryl and ethyl acrylate monomers: Hypotension and respiratory depression.

False Nail Remover

- Nitroethane: Methemoglobinemia.

False Nail Glue Remover

- Acetonitrile and propionitrile: Delayed (3–24 hours) CN poisoning due to hepatic P450 bio-transformation to an aldehyde and cyanide.
- Acetone: Dermal defatting.

Hair Relaxers and Straighteners

- Thioglycolates: Alkalis causing severe dermal and mucosal irritation and burns.
- Neutralizers and setting agents.
- Bromates: Severe vomiting, abdominal pain, and bloody diarrhea in 1–2 hours; then hypotension with resulting oliguria may cause acute tubular necrosis (ATN), permanent deafness, resembling aminoglycoside, toxicity may also occur.
- Treatment: Na thiosulfate to reduce bromates to less toxic bromides; hemodialysis.

Depilatories

- Barium sulfide: Severe hypokalemia, nausea, vomiting, diarrhea, hypertension, numbness, weakness, respiratory paralysis.
- Treatment: MgSO_4 to promote formation of nontoxic, insoluble barium sulfate (BaSO_4), frequently used as an oral or rectal radiographic contrast agent.

Button Batteries

- Uses: Hearing aids, watches, calculators, laser pointers, computer games.
- Contents: Combine heavy metal salts (Ni-Cd, Li, Cu, Hg, Zn) and a caustic alkali (NaOH, KOH). Lithium-containing batteries are the most toxic.
- Pathology: Caustic leakage can cause mucosal burns, pressure necrosis can cause gastrointestinal perforation, electrical gradients across moist mucosa may cause shocks with muscle stimulation.
- Diagnosis: Immediate AP/lateral chest and abdominal x-rays.
- Epidemiology: 86% of battery ingestions complete gastrointestinal transit in 4 days.

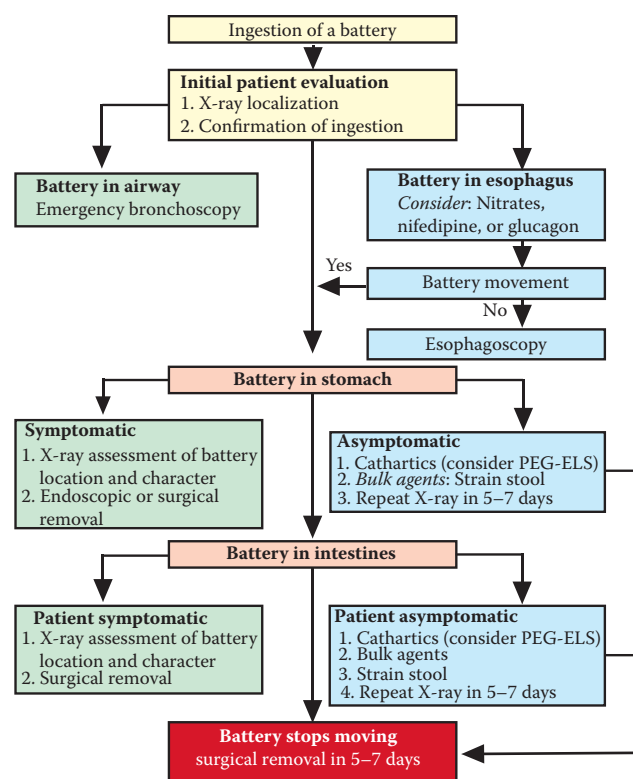


FIGURE 7.4 The management of battery ingestion. A clinical flow chart that describes the management of button battery ingestion. Although most ingested button batteries will traverse the gastrointestinal tract in 4 days, batteries that are aspirated into the lungs should be removed immediately at bronchoscopy, and batteries that become lodged in the gastrointestinal tract should be removed surgically by 5–7 days.

Toxic Alcohols

Anion Gap Metabolic Acidosis

- Definition: $[\text{Measured cations} - \text{measured anions}] = [\text{Na}^+] - [\text{Cl}^- + \text{HCO}_3^-] = 140 - [110 + 24] = 6$.
 - Normal range: 3–11.
 - High: MMUDPPIILEESS = Methanol, Metformin, Uremia, Diabetic ketoacidosis, Paraldehyde, Phenformin, INH, Iron, Lactic acidosis, Ethanol, Ethylene glycol, Salicylates, and Solvents. MMETAL ACCIID GAPP = Methanol, Metformin, Ethylene glycol, Toluene, Alcohol ketoacidosis, Lactic acidosis, Aspirin, Carbon monoxide, Cyanide, Isoniazid, Iron, Diabetic ketoacidosis, Generalized seizures, Aminoglycosides, Paraldehyde, Phenoformin.
 - Low: Bromides (falsely elevated anionic chloride levels).

Osmol Gap Metabolic Acidosis

- Definition: $[\text{Measured osmolality}] - [\text{calculated osmolality}] = [\text{mOsm/kg}] - [2\text{Na}^+ + \text{Glu}/18 + \text{BUN}]$
 - Normal range: –14 to +10
 - Abnormal: >10, an unknown low-molecular-weight osmotically active agent (usually a toxic alcohol) is present in serum.
 - High: Ethanol, all toxic alcohols, lactic acidosis, renal failure, hyperlipidemias, hypertriglyceridemias, and hyperproteinemias (multiple myeloma).

Ethanol (EtOH)

EtOH Pharmacology and Toxicity

- Chemistry: Colorless, odorless hydrocarbon; highly water soluble and highly lipid soluble; dependence and addiction possible.
- Pharmacology: Low molecular weight, low volume of distribution (V_d) = 0.6 L/kg, rapidly diffusible; rapid gastric emptying and drinking

without food increase absorption; hepatically oxidized by three pathways:

- Pathway 1: Alcohol dehydrogenase (ADH) $[\text{EtOH} \rightarrow (\text{ADH}) \rightarrow \text{Acetaldehyde} (\text{acetaldehyde dehydrogenase}) \rightarrow \text{Acetyl CoA} \rightarrow (\text{thiamine cofactor}) \rightarrow \text{Kreb's tricarboxylic acid (TCA) cycle} \rightarrow \text{CO}_2 + \text{H}_2\text{O}]$.
- Pathway 2: CYP-450 (inducible metabolism).
- Pathway 3: hepatic peroxidase-catalase.
- Toxicity: CNS > gastrointestinal > metabolic.
 - CNS: Inebriation, disinhibition, incoordination, blurred vision, diplopia, confusion, CNS and respiratory depression.
 - Gastrointestinal: Nausea, vomiting, cramping abdominal pain, gastric bleeding.
 - Metabolic: High anion gap metabolic acidosis, high osmolal gap metabolic acidosis, hypoglycemia, hypokalemia, hypomagnesemia, hypophosphatemia, hyperamylasemia.

Acute EtOH Intoxication: Blood Ethanol Levels

- 0.05% (50 mg/dL)
- 0.08% (80 mg/dL)*
- 0.10% (100 mg/dL)
- 0.20% (200 mg/dL)
- 0.30% (300 mg/dL)
- 0.40% (400 mg/dL)
- 0.70% (700 mg/dL)

[* Legally intoxicated in most U.S. states.]

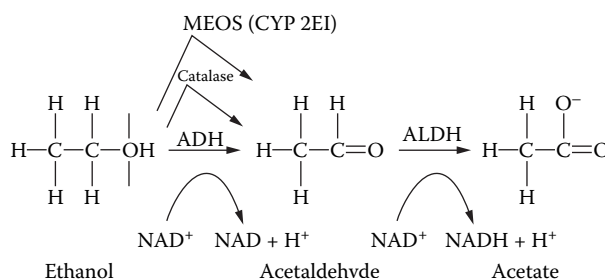


FIGURE 7.5 Ethanol metabolism. The hepatic biotransformation reactions, which are responsible for the metabolism of ethanol.

Clinical Manifestations

- Disinhibition and incoordination
- Decreased reaction time, auto driving impaired
- Nausea, vomiting, confusion, staggering gait
- Slurred speech, reduced vision, and reduced sensation
- Hypothermia, hypoglycemia, amnesia, seizures, hyporeactive deep tendon reflexes (DTRs), respiratory depression, loss of airway protective reflexes, aspiration pneumonia, coma, death

Diagnosis: EtOH Overdose

- Blood ethanol levels: Determine stage of intoxication.
- Blood glucose: Rule out hypoglycemia.
- CBC and lytes: Decreased Na, K, Mg, Ca, and P.
- ABGs: High-anion gap metabolic acidosis, increased osmolal gap.
- Serum amylase: Rule out pancreatitis.
- Serum ammonia: Rule out hepatic encephalopathy from alcoholic cirrhosis with acute liver failure.

Management: EtOH Overdose

- Ipecac contraindicated.
- Orogastric lavage and AC: Especially for co-ingestions.
- Coma cocktail: D₅₀W 0.5–1.0 g/kg + thiamine 100 mg IV.
- Multivitamins and folate 1–5 mg IV.
- Slow rewarming.
- Correct electrolytes: Low K-Mg-P.
- Enhanced elimination: Hemodialysis very effective given ethanol's low molecular weight and volume of distribution, but rarely indicated.

EtOH: Antabuse (Disulfiram) Reactions

- Antabuse (disulfiram) reaction: Flushing, diaphoresis, nausea, vomiting, disorientation, vertigo, headache, palpitations, chest pain mimicking acute myocardial infarction (MI).
- Precipitated by antibiotics: Chloramphenicol, n-MTT side chain cephalosporins, sulfonamides.

- Precipitated by antifungals: Griseofulvin, metronidazole.
- Mimicked by *Mickey Finn*: Chloral hydrate (and its trichloroethanol metabolite).
- Miscellaneous: *Coprinus* spp. mushrooms (*Coprinus atramentarius*), industrial chemicals: carbamate pesticides and oximes.

Isopropanol

Isopropanol Pharmacology and Toxicity

- Chemistry: 70% isopropyl alcohol or rubbing alcohol; a clear, colorless volatile liquid with an acetone smell; used in toiletries, disinfectants, window cleaners, and solvents. Exception: the only alcohol adsorbed by AC (activated charcoal).
- Pharmacology: Rapid all-route absorption, especially dermal and inhalation; low volume of distribution = 0.6 L/kg; 50% rapidly metabolized by alcohol dehydrogenase (ADH) to acetone, remaining 50% unmetabolized and excreted by kidneys > exhalation via lungs.
- Toxicity: CNS > gastrointestinal > pulmonary > metabolic:
 - CNS: Three times more CNS depression than EtOH, lethargy, weakness, headache, ataxia, dysarthria, confusion, apnea, respiratory depression, hypotension.
 - Pulmonary and gastrointestinal: Acetone breath, hemorrhagic gastritis and hemorrhagic tracheobronchitis.
 - Metabolic: Exception: only toxic alcohol not causing metabolic acidosis or hypoglycemia; euglycemia is maintained; ketonemia and ketonuria occur from acetone poisoning.

Diagnosis: Isopropanol Overdose

- Determine serum acetone level.
- Anticipate falsely elevated creatinine.
- Arterial blood gases: pH will be normal, no metabolic acidosis.
- Glucose: No hypoglycemia.
- Anticipate ketonemia and ketonuria from acetone metabolites.
- Breath: Acetone odor.

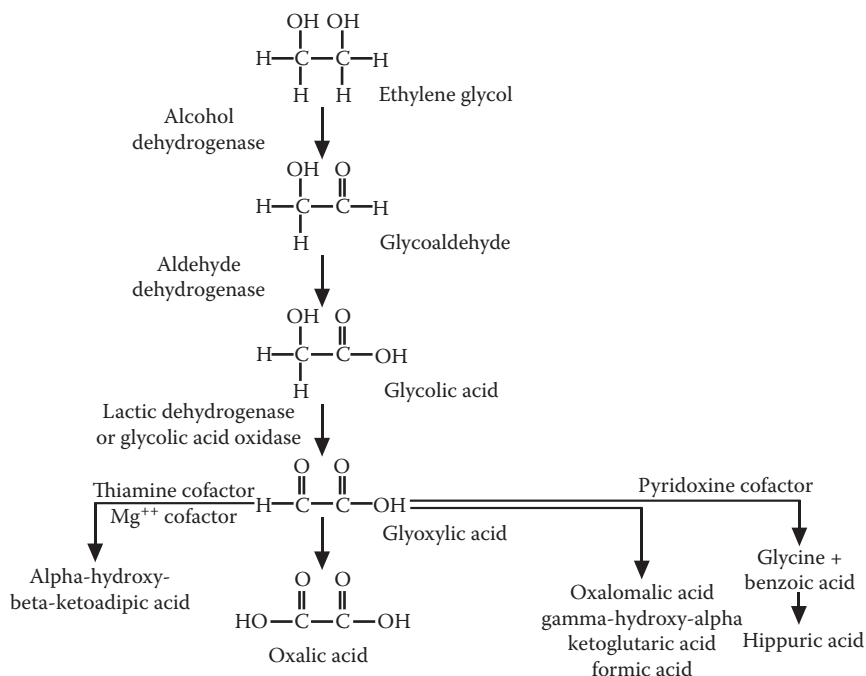


FIGURE 7.6 Ethylene glycol metabolism. The hepatic biotransformation reactions, which are responsible for the metabolism of ethylene glycol, a common component of antifreeze.

Management: Isopropanol Overdose

- Immediate skin decontamination.
- Orogastric lavage, then AC: Exception: only toxic alcohol to be well adsorbed by AC.
- Enhanced elimination: Hemodialysis very effective in serious overdoses, especially in children. Ethanol is not indicated because there is no need to block isopropanol's metabolism to acetone, which is relatively nontoxic and exhaled by the lungs and excreted in the urine.

Ethylene Glycol (EG)

EG Pharmacology and Toxicity

- Chemistry: A toxic alcohol similar to methanol in toxicity and lethality, with a characteristic delayed onset of toxicity; used in antifreeze (95%), refrigerating fluids, fire extinguishers, solar energy fluids.
- Pharmacology: Rapidly absorbed orally, peaks within 1–4 hours; rapidly metabolized by ADH to glycoaldehyde and by the glycoaldehyde dehydrogenase to its toxic metabolites, glycolic, glyoxylic, and oxalic acids. Pyridoxine and thiamine can serve as cofactors to promote nontoxic alternative routes of metabolism.
- Toxicity: (1) CNS > (2) Metabolic > (3) Renal > Initial gastrointestinal toxicity: nausea and vomiting;

— Toxic phases 1–3:

- Phase 1, CNS: Ataxia, nausea, vomiting, intoxication, inebriation, nystagmus, myoclonus, seizures, progressing to lethargy and coma within 4 to 8 hours.
- Phase 2, Cardiovascular and metabolic: Profound high anion gap metabolic acidosis progressing to hypertension, tachycardia, tachypnea, and cardiovascular collapse.
- Phase 3, Renal: Urinary excretion of toxic metabolites, especially oxalate, which combines with calcium to form calcium oxalate crystals (calcium oxalate and hippuric acid); with calcium oxalate crystalluria causing nephrolithiasis, proteinuria, and hematuria, and may progress to acute tubular necrosis.

EG Overdose: Diagnosis and Management

- Diagnosis: Calcium oxalate crystalluria, urine fluorescein staining under ultraviolet Wood's lamp lighting, serum EG levels by gas chromatography.
- Initial management: AC ineffective due to rapid absorption and delayed symptom onset of 4–8 hours; ipecac contraindicated due to existing vomiting; sodium bicarbonate (NaHCO₃) to correct acidosis and increases excretion of weak acids; antidotes = ethanol (and/or 4-methylpyr-

azole [4-MP], an alcohol dehydrogenase inhibitor) as preferred ADH substrates, 0.8 g/kg IV or 8 mL/kg orally, to maintain serum EtOH level of 100–150 mg/dL (EG:EtOH ratio = 1:4).

- Enhanced elimination: (1) Urinary alkalization to promote urinary excretion of weak acid metabolites; (2) thiamine (100 mg IV) and pyridoxine (50 mg IV) every 6 hours, to promote alternative nontoxic routes of metabolism; (3) hemodialysis for EG levels >25 mg/dL.
- Correct hypocalcemia: Treat hypocalcemia from massive calcium losses in calcium oxalate crystalluria.

EG Ingestion

- Urinary calcium oxalate crystals (ethylene glycol ingestion requires ethanol and/or 4-methylpyrazole (fomipazole, 4-MP) therapy, often with hemodialysis (HD) for serum EG levels >25 mg/dL to prevent acute tubular necrosis (ATN).

Methanol (MeOH)

MeOH Pharmacology and Toxicity

- Chemistry: Methyl alcohol or wood alcohol; used in windshield washing fluids, deicing solutions, carburetor cleaners, model airplane glues, canned heat (Sterno®) fuels, paint removers/thinners.
- Pharmacology: Rapid all-route absorption, peaks 1/2–1 hour; 85% rapidly metabolized by hepatic alcohol dehydrogenase (ADH) to formaldehyde and formic acid metabolites that are responsible for retinal toxicity.
- Toxicity: Eye/CNS > Metabolic > Initial gastrointestinal toxicity: nausea, vomiting, and cramping:
 - Eye: Dimmed and blurred vision, scotomata, dilated and sluggishly reactive pupils, hyperemic optic discs, retinal edema, blindness.
 - CNS: Inebriation, headache, vertigo, meningismus, cerebral edema, seizures, coma.
 - Metabolic: 24-hour delayed onset of high-anion gap metabolic acidosis, followed by oculotoxicity.

MeOH Overdose: Diagnosis and Management

- Diagnosis: Lactic acidosis, unique eye findings, increased serum methanol levels by gas chromatography.
- Initial management: AC ineffective due to rapid absorption and delayed symptom onset; ipecac contraindicated due to vomiting; NaHCO₃ to correct acidosis; antidotes = ethanol (and/or fomipazole [4-MP]) as preferred ADH substrates, 0.8 g/kg IV or 8 mL/kg orally, to maintain serum EtOH level 100–150 mg/dL (MeOH: EtOH ratio = 1:4).
- Enhanced elimination: (1) Urinary alkalization to promote renal excretion of undissociated formic acid; (2) folic acid, 150 mg IV every 4 hours, to serve as a cofactor promoting the metabolism of formic acid to CO₂ + H₂O; (3) hemodialysis for methanol levels >25 mg/dL.

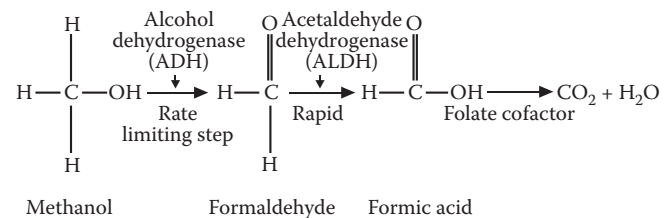


FIGURE 7.7 Methanol metabolism. The hepatic biotransformation reactions, which are responsible for the metabolism of methanol or wood alcohol.

TABLE 7.6 The Pathophysiology and Management of Toxic Alcohol Poisonings

Alcohol	Uses	Toxic Dose	Action Level	Metabolism	Manifestations	Management
Isopropanol (rubbing alcohol)	Rubbing alcohol, nail polish remover	2–4 mL/kg	NA	Metabolized by ADH to acetone — exhale or urine secreted	Ketosis without acidosis, inebriation, ataxia, dysarthria, confusion, stupor, coma, acetone breath, hemorrhagic gastritis	Supportive, no ethanol
Ethylene glycol (antifreeze)	Antifreeze, coolants, brake fluids	1–1.5 mL/kg	>20–20 mg/dL	Metabolized by ADH to glycolic and oxalic acids. Oxalate combines with calcium to cause calcium oxalate crystalluria.	Increased anion and decreased osmolal gaps, hypocalcemia with and increased QT and tetany; CNS (1–12 hour): ataxia, nystagmus seizures, nausea-vomiting; Cardiovascular/Metabolic (12–27 hours): hypertension, tachycardia, increased QT, tachypnea, cardiovascular collapse Renal (24–72 hours/ cardiovascular) tenderness, oliguria, urine fluorescein, acute renal failures	Alkalinize urine, thiamine, and pyridoxine, to promote nontoxic metabolism, ethanol IV or 4-methylpyrazole, orally, hemodialysis
Methanol (wood alcohol)	Windshield washer, radiator fluid, Sterno® fuel	<1 mL/kg	>50 mg/dL	Metabolized by ADH to formaldehyde and formic acid	Increased anion and osmolal gaps, intoxication. Nausea-vomiting, hemorrhagic gastritis, photophobia, blurred – reduced vision, “snowfield” blindness, retinal edema, hyperemic optic disks	Alkalinize urine, folic acid, to promote nontoxic metabolism, ethanol IV, hemodialysis

Toxic Deafness and Blindness

Reversible vs. Irreversible Neurotoxic Deafness

Reversible Neurotoxic Deafness
May Be Caused By:

- Antibiotics (quinine > erythromycins)
- Carbon monoxide
- Diuretics
- Salicylates and NSAIDs

Irreversible Neurotoxic Deafness May Be Caused By:

- Aminoglycosides
- Bromates
- Hydrocarbons (toluene > xylene, styrene)
- Heavy metals (Hg > As)

Ototoxicity from Aminoglycoside Antibiotics

Can Be Characterized By:

- Permanent cochlear and vestibular hair cell degeneration (deafness and vertigo)
 - Gentamicin
 - Tobramycin
- Cochlear toxicity alone (deafness only)
 - Amikacin
 - Kanamycin
 - Neomycin
- Permanent vestibular hair cell degeneration (vertigo only)
 - Streptomycin

Neurotoxic Blindness

Neurotoxic Blindness May Be Caused By:

- Most common causes: methanol, quinine.
- Less common causes: antihypertensives (cortical blindness), carbon monoxide, cocaine (retinal vasospasm), ergots (retinal vasospasm), hydrogen sulfide.

Reproductive and Perinatal Toxicology

Chapter Outline

Epidemiology of reproductive toxicology

Toxins affecting fertility, potency, and gestation

- Toxic priapism and abortifacients

Pharmacokinetics of pregnancy

- Factors promoting increases in free drug concentration
- Factors promoting decreases in free drug concentration
- Placental transfer

Acute poisoning in pregnancy

- Epidemiology
- General management
- Neonatal toxicokinetics

Specific poisonings in pregnancy

- Acetaminophen (APAP) overdose in pregnancy
- Iron overdose in pregnancy
- Maternal carbon monoxide (CO) poisoning

Theophylline overdose in pregnancy

- Pharmacology
- Toxicity
- Theophylline metabolism
- Management: theophylline overdose
- Specific management: theophylline overdose
- Theophylline enhanced elimination

Substance abuse in pregnancy

- Alcohol abuse and Fetal Alcohol Syndrome (FAS)
- Cocaine abuse and Fetal Cocaine Syndrome (FCS)
- Opioid abuse in pregnancy
- Neonatal Withdrawal Syndrome (NWS)

Breast-feeding

- Toxicokinetics
- Absolutely contraindicated drugs in breast-feeding mothers
- Relatively contraindicated drugs

Epidemiology of Reproductive Toxicology

- There are more than 90,000 chemicals used commercially in the United States, but only 2200 have been evaluated for mutagenic and teratogenic effects in animal models.
- There are more than 20 million women of reproductive age in the U.S. workforce, but only 4 to 6% of birth defects are related to known drug or toxin exposures during pregnancy.
- From 30 to 70% of pregnant women use three to ten different drugs during pregnancy, especially vitamins, iron, analgesics, antipyretics, antimicrobials, antiemetics, theophylline, caffeine, ethanol, and nicotine.
- From 15 to 25% of pregnant women report licit drug use (ethanol > nicotine), or illicit drug use (marijuana > cocaine > heroin), or have positive urine drug screens during pregnancy.
- Analgesics, vitamins, iron, antibiotics, theophylline, and psychotropic medications account for 50 to 80% of all reported toxic ingestions by pregnant women.

Toxins Affecting Fertility, Potency, and Gestation

TABLE 8.1 Male Infertility

Drugs or Toxins	Mechanisms of Infertility
Anabolic steroids	Low luteinizing hormone (LH, impair Leydig cells) levels, low sperm number, and abnormal sperm morphology
Androgens	Low testosterone, low sperm counts
Antineoplastics	Direct gonadal toxicity, spermatogenesis ceases levels
Carbon disulfide	Low luteinizing hormone levels, low follicle stimulating hormone levels (FSH, impair Sertoli cells), low sperm counts
Cimetidine	Low sperm counts
1,2-Dibromo-3-chloropropane	Low sperm counts
Epichlorohydrin	Low sperm counts
Ethanol	Low testosterone, low sperm counts
Ethylene dibromide	Low sperm counts
Lead	Low sperm counts
Opioids	Low luteinizing levels, low testosterone levels, low sperm counts
Sulfasalazine	Low sperm counts
Marijuana and tobacco	Low testosterone levels, low sperm counts

TABLE 8.2 Male Sexual Dysfunction

Drugs or Toxins	Mechanisms of Dysfunction
Anabolic steroids	Low libido, impotence
Anticholinergics	Erectile failure
Antihypertensives (α_2 -agonists)	Impotence, erectile failure (neurologic)
Antihypertensives (thiazides)	Erectile failure (vascular)
Cimetidine	Low libido, impotence
Dimethylaminopropionitrile	Neurogenic bladder, erectile failure
Ethanol	Impotence, erectile failure
Lead	Low libido, erectile failure
Lithium	Erectile failure
MAOIs	Low libido, impotence
Opioids	Low libido
Phenothiazines	Low libido
TCAs	Low libido, impotence

TABLE 8.3 Female Infertility

Drugs or Toxins	Mechanisms of Infertility
Anabolic steroids	Low luteinizing hormone and follicle stimulating hormone levels
Antineoplastic agents	Direct gonadal toxicity, oogenesis ceases
Carbon disulfide	Low luteinizing hormone and follicle stimulating hormone levels
Lead	Increased spontaneous abortions and stillbirths
Oral contraceptives	Prolonged hypothalamic-pituitary axis shutdown, panhypopituitarism
Thyroid hormone	Increased anovulatory cycles

TABLE 8.4 Female Sexual Dysfunction

Drugs or Toxins	Mechanisms of Dysfunction
Anabolic steroids	Low libido
Cimetidine	Low libido
Lithium	Low libido
Opioids	Low libido
Oral contraceptives	Low libido
Phenothiazines	Low libido
Tricyclic antidepressants	Low libido
SSRIs	Low libido

TABLE 8.5 Aphrodisiacs

Drugs or Toxins ("street names")	Mechanisms of Toxicity
Bufotoxins: bufotalin, bufotenine; dried toad skin venom = "love stone," "rock hard"	Cardiac glycoside (digitalis) toxicity. Treatment = digoxin Fabs (DigiBind®)
Cantharidin: crushed blister beetle = "Spanish fly"	Hemorrhagic blistering of mouth, gastrointestinal and genitourinary tracts; hemorrhagic bladder bullae; priapism; vaginal bleeding
Lead additives: for red color	Lead colic, anemia, basophilic stippling, infertility, impotency, spontaneous abortion, still birth
Nitrites: amyl (crushable-"pop" sound), butyl, isobutyl = "poppers"	Headache, nausea, syncope, hypotension, reflex tachycardia, methemoglobinemia
Yohimbine: African yohimbe tree bark extract, an α_2 -antagonist and cholinergic agonist = "yo yo"	Unopposed α_1 -mediated hypertension, tachycardia, myocardial infarction, mydriasis, diaphoresis, flushing; cholinergic-SLUDE and flushing; treatment = AC decontamination, then benzodiazepines (BZs)

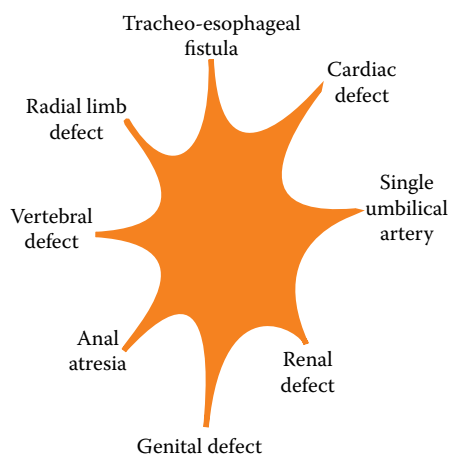


FIGURE 8.1 The VACTREL association 1. The VACTREL association is a constellation of birth defects that may occur in the rare pregnancies conceived during maternal birth control with oral contraceptive pills. The mnemonic VACTREL stands for vertebral anomalies (spina bifida), imperforate anus, congenital cardiac defects, tracheo-esophageal fistula, and limb deformities (radial agenesis or dysplasia).

Toxic Priapism and Abortifacients

Priapism-Inducing Agents

- α -blockers and vasodilators — mechanism: Erection = cholinergic stimulation (increases blood in) + α_2 -antagonism (decreases blood out):
 - Guanethidine (α_2 -antagonism)
 - Hydralazine (α_2 -antagonism)
 - Labetalol (α_2 -antagonism)
 - Phenothiazines (α_2 -antagonism)
 - Prazosin (α_2 -antagonism)
 - Trazadone (α_2 -antagonism)
 - Yohimbine (α_2 -antagonism)
- Miscellaneous:
 - Androgens
 - Anticoagulants
 - Cantharidin
 - Nitric oxide agonists

Abortifacients

- Quinine: Oxytocic anti-malarial.
- Misoprostol: Synthetic $\text{PGE}_{2\alpha}$, oxytocic used for therapeutic abortions.
- Mifepristone (RU 486): “Morning-after” pill (Plan B®), an antiprogesterone that must be combined with PGE for therapeutic abortions.

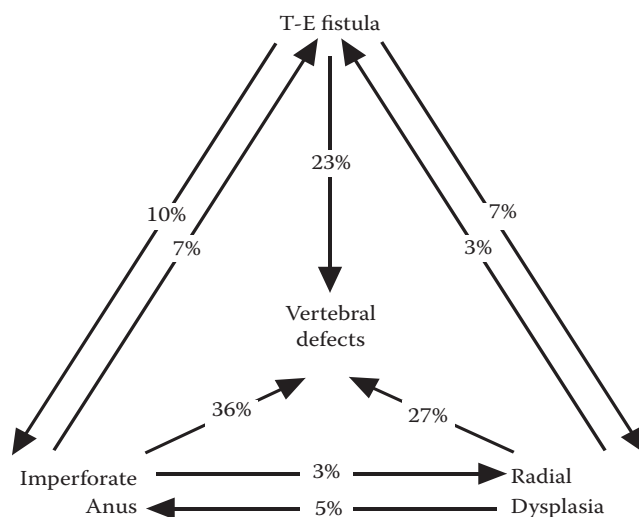


FIGURE 8.2 The VACTREL association 2. A diagram that indicated the ranges of joint association of congenital birth defects in the VACTREL association.

- Pulegone (pennyroyal oil): Hepatotoxicity from glutathione depletion (like APAP).
 - Treatment: N-acetylcysteine (NAC).
- Black cohosh root: Herbal preparation causing gastrointestinal and genitourinary mucosal toxicity.

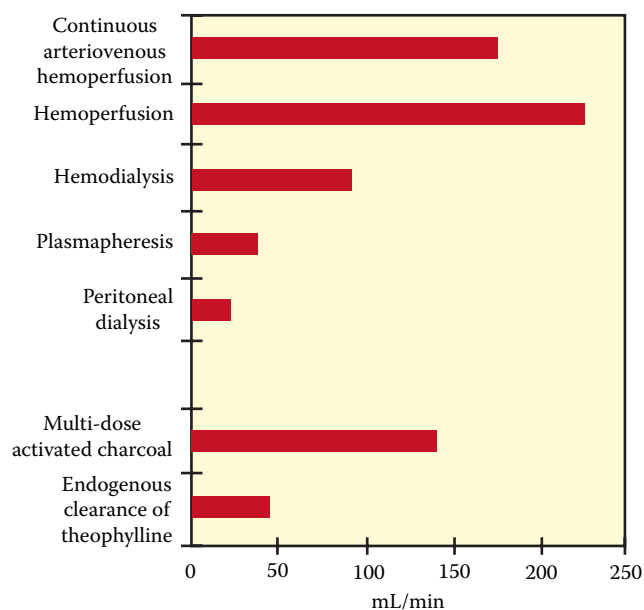


FIGURE 8.3 Theophylline overdose in pregnancy. Hemoperfusion offers the most rapid method for extra-corporeal clearance of theophylline when ingested in toxic amounts during pregnancy.

Pharmacokinetics of Pregnancy

Factors Promoting Increases in Free Drug Concentration

Increased Drug Absorption

- Reduced gastric emptying times
- Reduced gastrointestinal tract motility
- Increased gastrointestinal content–mucosal contact times
- Increased skin and mucosal perfusion
- Increased respiratory rate (RR) and tidal volume (TV)

Increased Drug Distribution

- High cardiac output
- Reduced protein (albumin) binding
- Reduced hepatic biotransformation
- Increased free fatty acids (FFAs), which release stored lipophilic drugs (benzodiazepines) and displace bound drugs

Factors Promoting Decreases in Free Drug Concentration

Increased Drug Excretion

- Increased extracellular fluid volume (ECFV)
- Increased renal blood flow (RBF)
- Increased glomerular filtration rate (GFR)
- Increased urine output

Placental Barrier Effect

- Placental biotransformation of drugs
- Placental ion trapping of acidic drugs

Placental Transfer

FDA Use-in-Pregnancy Ratings

- A — Human randomized control trials (RCTs) show no risk
 - Example: prenatal vitamins (except vitamins A, E, and D in high doses)
- B — Animal studies show no risk
 - Example: Acetaminophen (APAP)
- C — Risk in humans uncertain
 - Example: Albuterol
- D — Clear evidence of risk in humans
 - Example Tetracyclines
- E — Use in pregnancy is contraindicated
 - Example: Isoretinoin
- X — Known teratogen
 - Example: Iodine, quinine

Mechanisms of Placental Transfer

- Factors promoting increased passive diffusion across the placental barrier:
 - Low molecular weight
 - High lipid solubility
 - Low ionization
 - Reduced protein binding
- Ion trapping of weak acids in the lower pH of fetus (7.25–7.30): Valproate (valproic acid), phenytoin, isoretinoin (isoretinoic acid), thalidomide.
- Near-term maternal changes: Increased levels of free fatty acids (FFAs) release maternal fat-stored drugs. Example: benzodiazepines (BZs).
- Near-term fetal changes: Increased serum albumin = increased fetal drug binding near term.

FDA Category E and X Drugs

FDA Category E =
Contraindicated Drugs → Fetal Outcomes:

- Aminoglycosides: Deafness

- Anticonvulsants: Craniofacial defects (CFDs) and neural tube defects (NTDs)
- Antineoplastics: Chromosomal damage and mutations
- Antithyroids, iodine: Neonatal hypothyroidism (cretinism) and goiter
- NSAIDs: Premature closure of the patent ductus arteriosus (PDA)
- Progestogens and androgens: Female masculinization
- Sulfonamides: Neonatal jaundice and kernicterus
- Sulfonylureas: Neonatal hypoglycemia

FDA Category X =

Known teratogens → Fetal Outcomes:

- Carbamazepine: CFDs and NTDs
- Cocaine: Intrauterine growth retardation, ischemic limb reduction, and autoamputation
- Coumarins: Fetal warfarin syndrome
- Diethyl-stilbesterol (DES): Vaginal adenosis and cancer

- Ethanol: Fetal alcohol syndrome, CFDs
- Lithium: Ebstein's anomaly
- Misoprostel: Short limbs, Moebius syndrome
- Methotrexate: CFDs
- Methyl mercury: Minimata disease
- Phenytoin and retinoids: CFDs
- Tetracyclines: Dark teeth staining
- Thalidomide: Phocomelia
- Valproate: CFDs and NTDs

Teratogenic Syndromes

- Fetal Hydantoin Syndrome
- Fetal Valproate Syndrome
- Moebius Syndrome (vascular disruption of limbs secondary to misoprostel and cocaine)
- Minimata Disease (congenital methyl mercury poisoning)
- Fetal Isoretinoin Syndrome (Accutane® embryopathy)
- Fetal Warfarin Syndrome

Acute Poisoning in Pregnancy

Epidemiology

- 2–12% of women who attempt suicide are pregnant.
- 1–5% of pregnancy deaths are results of overdose suicides with over-the-counter and prescription medications.
- Analgesics, vitamins, iron, psychotropics, and theophylline account for 50–79% of drug overdoses in pregnancy.
- Warning: Chronic exposures to ethanol and most anticonvulsants will cause CFDs (carbamazepine, phenytoin, valproate) and/or NTDs (valproate).

General Management

- Ipecac is contraindicated due to excessive vomiting-induced risk of preterm labor.
- Coma cocktails should contain dextrose and naloxone.
- Activated charcoal (AC) is very useful because of gastric axis shift with gastric content stasis.
- Whole-bowel irrigation (WBI) with polyethylene glycol-electrolyte solution (PEG-ELS) is indicated for iron (Fe) overdose to flush out slow-release tablets; Fe is not AC-adsorbed.
- Most antidotes are FDA category C or better; only ethanol is category D.
- Never withhold specific antidotes in pregnancy, especially NAC for acetaminophen (APAP) overdose, a commonly ingested suicidal agent.

Neonatal Toxicokinetics

- Increased dermal absorption: Hexachlorophene-vacuolar encephalopathy, aniline dyes may cause methemoglobinemia (MetHb), iodine-containing antiseptics may cause hypothyroidism.
- Increased protein binding: Sulfonamides and ceftriaxone displace bilirubin from albumin and cause kernicterus in neonates.
- Reduced hepatic P-450 metabolism: High concentrations of phenytoin, phenobarbital, theophylline cause reduced glucuronidation of chloramphenicol with resulting *gray baby* syndrome; benzyl alcohol = *gasping baby* syndrome.
- General management: No ipecac or lavage due to existing electrolyte and temperature losses; consider exchange transfusion > hemodialysis > hemoperfusion for drug overdoses.

Specific Poisonings in Pregnancy

Acetaminophen (APAP) Overdose in Pregnancy

- Epidemiology: The most commonly used and overdosed analgesic in pregnancy.
- Mechanisms: Rapid glutathione depletion first in mother and then in fetus, with generation of hepatotoxic *n*-acetyl-*para*-benzoquinoneimine (NAPQI) metabolite; mother > fetus.
- Management: N-acetylcysteine (NAC).
- Warning: Consider induction in late third trimester due to high case fatality rates (CFRs). Spontaneous abortion or preterm labor often occur within weeks of successful treatment with NAC.

Iron Overdose in Pregnancy

- Epidemiology: Another common overdose in pregnancy; maternal > fetal toxicity, with maternal fatalities resulting from placental barrier blocking large Fe transfers to fetus.
- Mechanisms: Most Fe remains in the maternal circulation and can be chelated with deferoxamine, which is only minimally transferred across the placenta.
- Management: Initial deferoxamine chelation; whole-bowel irrigation (WBI) with polyethylene glycol-electrolyte solutions (PEG-ELS) for massive and slow-release Fe tablet overdoses as Fe is not adsorbed to AC.

Maternal Carbon Monoxide (CO) Poisoning

- Epidemiology: CO is the leading cause of all poison fatalities; fetal > maternal toxicity and fatality.
- Mechanisms: (1) Fetus has 10–15% higher baseline carboxyhemoglobin (COHb) levels than mother; (2) in CO poisoning, fetus develops 58% higher CO levels than mother; (3) both maternal and fetal PO₂s reduced by COHb, fetal (normal fetal PO₂ = 20–30 mmHg) > mother; (4) left shift of O₂Hb dissociation curve provides reduced tissue O₂; (5) cellular hypoxia results from inhibition of mitochondrial cytochrome oxidase.
- Management: Hyperbaric oxygen therapy.

Theophylline Overdose in Pregnancy

Pharmacology

- Serum levels: Therapeutic levels 5–15 mcg/mL; toxic >20 mcg/mL; hemoperfusion indicated levels >90 mcg/mL anytime; and >40 mg/mL with seizures, arrhythmias, refractory vomiting, or hypotension.
 - Mechanisms: Antagonizes adenosine to diminish histamine release and inhibits phosphodiesterase to increase cAMP activity and release catecholamines promoting bronchodilation and reversing bronchospasm = smooth muscle relaxation, peripheral vasodilation, sympathetic cardiovascular and CNS stimulation.
 - Metabolic: Low volume or distribution (0.5 L/kg); 50% protein bound; 90% P-450 biotransformed to inactive metabolites; 10% renal excretion.
- Primidone
 - Rifampin
 - Cigarette and marijuana smoking
 - Metabolism reduced by (toxicity possible):
 - Cimetidine
 - Quinolone antibiotics
 - Macrolide antibiotics
 - Mexilitene
 - Verapamil
 - Reduced hepatic perfusion:
 - Advancing age
 - Intercurrent infections
 - Congestive heart failure
 - Hepatic failure

Toxicity

- Forme fruste: Severe nausea and vomiting, tachyarrhythmias, seizures, hypotension, hypokalemia, metabolic acidosis.
- Cardiovascular: Tachyarrhythmias from β_1 stimulation, hypotension from β_2 stimulation.
- Gastrointestinal: Severe nausea and vomiting, hypokalemia, hypovolemia.
- CNS: Anxiety, tremor, agitation, hyperventilation, seizures — all resulting from loss of adenosine's anticonvulsant activity.
- Metabolic: Hypokalemia, hypocalcemia, hypophosphatemia, metabolic acidosis.

Theophylline Metabolism

- Metabolism increased by (lack of efficacy possible):
 - Carbamazepine
 - Phenobarbital
 - Phenytoin

Management: Theophylline Overdose

- Initial assessment:
 - ABCs and ECG monitoring.
 - Labs: Theophylline level, CBC, electrolytes, Ca, glucose, BUN, creatinine, clotting studies.
 - Avoid β -mimetics (high heart rate, hypotension).
 - Avoid ipecac and most antiemetics, especially phenothiazines (increased arrhythmias and required seizure threshold).
- Gastrointestinal decontamination:
 - Gastric emptying: No ipecac, granisetron > ondansetron (5-HT blockers) > metoclopramide for severe vomiting; hemoperfusion for refractory vomiting.
 - Orogastric lavage: Best to administer AC and sorbitol; lavage will be limited by slow-release tablets, bezoars, and concretions.
 - AC: 1–2 g/kg, + sorbitol (1 g/kg).
 - MDAC: 0.5 g/kg every 2 hours, no cathartics.
 - WBI (whole-bowel irrigation): For sustained-release preparations.
 - Consider hemoperfusion: For levels >40 mcg/mL, complicated by seizures, vomiting, hypotension, ventricular arrhythmias; definite hemoperfusion for levels >90 mcg/mL anytime.

Specific Management: Theophylline Overdose

- CNS Toxicity:
 - Agitation and restlessness, then seizures: D₅₀W + thiamine 100 mg for hypoglycemia; IV benzodiazepines (BZs) > barbiturates for seizures.
 - Refractory seizures: Secure airway; BZs and barbiturates; consider MRs; control ventilation; avoid phenytoin with quindine-like tachyarrhythmias.
 - Status epilepticus: Aggressive charcoal hemoperfusion to reduce theophylline levels <40 mcg/mL.
- CV toxicity:
 - Hypotension: Fluid load with normal saline or Ringer's lactate (RL); as vasopressors, use pure α -agonists, norepinephrine or phenylephrine, titrated to effect; avoid mixed agonists with potential for β_2 -mediated vasodilation and hypotension.
 - Tachydysrhythmias: Restore electrolyte balance, especially K and Ca; as antiarrhythmics, use adenosine and calcium channel blockers (CCBs) (verapamil, diltiazem) rather than β -blockers (bronchospasm, hypotension); consider lidocaine but it may reduce the seizure threshold; charcoal hemoperfusion for PVCs, which could precipitate VT.

Theophylline Enhanced Elimination

- Acute theophylline toxicity:
 - Acute charcoal hemoperfusion indications:
 - Theophylline level >90 mcg/mL at any time.
 - Theophylline level >40 mcg/mL when combined with:
 - Seizures
 - Hypotension, refractory to fluid loading
 - Ventricular dysrhythmias
 - Protracted vomiting, refractory to antiemetics
- Chronic theophylline toxicity:
 - Risks increase with advancing age, intercurrent illnesses/infections, and reduced hepatic perfusion.
 - No role for either emesis or orogastric lavage, unless to instill AC via orogastric tube.
 - AC and MDAC for cardiovascular-stable patients.
 - Charcoal HP for unstable patients and for AC failures.
 - Monitor theophylline levels every 4–6 hours until <20 mcg/kg.

Substance Abuse in Pregnancy

Alcohol Abuse and Fetal Alcohol Syndrome (FAS)

- Epidemiology: 20% of pregnant women consume alcohol; 1–2% consume >4 drinks/day; FAS = >2–3 ounces of ethanol/day (4–6 drinks/day) or with frequent binge drinking.
- Mechanism of FAS: Craniofacial dysmorphogenesis = early teratogenesis; mental retardation and cortical defects occur later in gestation.
- FAS: Intrauterine growth retardation (IUGR), microcephaly, epicanthal folds, short palpebral fissures, cleft palate, short philtrum — maxillary hypoplasia, micrognathia, mental retardation.

Cocaine Abuse and Fetal Cocaine Syndrome (FCS)

- Epidemiology: 1% of U.S. women use cocaine during pregnancy.
- Mechanism of FCS: Vasospastic and vascular disruptive effects on uteroplacental and fetal end circulations.
- FCS: Intrauterine growth retardation (IUGR), microcephaly, neurobehavioral abnormalities, vascular disruptive phenomena = limb autoamputation (Moebius syndrome), seizures, cerebral infarctions, visceral and genitourinary defects.
- OB complications: Abruptio placenta, premature delivery.

Opioid Abuse in Pregnancy

- Epidemiology: 0.2% of pregnant women use heroin > methadone; 75,000 neonates/year are exposed to opioid abuse *in utero* and 60–90% manifest neonatal withdrawal syndrome (NWS).
- Maternal complications: Hepatitis, sepsis, septic emboli, subacute bacterial endocarditis, STDs, AIDS.
- OB comp: Spontaneous abortion (SAB), premature delivery, stillbirth.
- Neonatal complications: Small for gestational age.
- Neonatal withdrawal syndrome (NWS): Occurs within 24 hours for heroin, but delayed for days with methadone abuse; increased incidence of sudden infant death syndrome (SIDS) for 2 years.

Neonatal Withdrawal Syndrome (NWS)

- Mechanism: Chronic opioid use leads to tolerance, dependence, and high number of CNS α_2 -receptors.
- Definition: WITTHDDRAAWAL = Wakefulness, Irritability, Tremulousness-low Temperature-Tachypnea, Hyperactivity-Hyperreflexia, Diarrhea-Diaphoresis, Rhinorrhea-Respiratory distress, Apnea-Autonomic dysfunction, Weight loss, Alkalosis (respiratory), and Lacrimation.
- Treatment: Tincture of opium (paregoric) for withdrawal seizures.

Breast-Feeding

Toxicokinetics

- Only free drugs are available for transfer from maternal plasma to breast milk.
- Membrane diffusion factors determine transfer: Low molecular weight, increased lipid solubility, decreased ionization, and limited protein binding all promote diffusion across membrane barriers.
- Lipid solubility = number-one determinant of milk transfer.
- High-molecular-weight drugs, like heparin and insulin, do not transfer.
- Breast milk, with a lower pH = 7.0, will concentrate weak bases, like sulfacetamide.

Absolutely Contraindicated Drugs in Breast-Feeding Mothers

- Bromocriptine: Decreased lactation
- Antineoplastics and radiopharmaceuticals: Carcinogenesis, myelosuppression, immunosuppression
- Ergotamines: Increased neonatal vomiting and seizures
- Lithium
- Metronidazole
- Substances of abuse
- Chloroamphenicol: Gray-baby syndrome

Relatively Contraindicated Drugs

- Phenobarbital
- Sulfonamides: Hemolysis in G-6-PD deficient neonates

Poisonings with Analgesic Adjuvants, Psychotropics, Sedative-Hypnotics, and Illicit Substances

Part 1:

Analgesic Adjuvants, Psychotropics, and Sedative-Hypnotics: Outline

Caffeine

- Pharmacology
- Physiology
- Therapeutic uses
- Toxicities
- General Overdose Management

Ergotamines

- Pharmacology
- Physiology
- Therapeutic uses
- Ergotism
- General overdose management

Cyclic antidepressants (CAs)

- Epidemiology
- Pharmacology
- First generation vs. second generation
- Toxicity

SSRIs vs. Neuroleptics

- Diagnosis and management

Monoamine oxidase inhibitors

- Pharmacology
- Toxicity
- MAOIs and drugs
- MAOIs and foods

Neuroleptics

- Classification

- Pharmacology
- Toxicology
- Overdose

Lithium

- History
- Pharmacology
- Toxicity
- Overdose
- Enhanced elimination

Anticonvulsants

- Classification
- Sodium channel blockers
- GABA inhibition enhancers
- Combined sodium channel blockers and GABA enhancers

Sedative-hypnotics

- Definitions
- Classification
- Mechanism
- Pharmacology

Diagnosis

- Overdose management
- Bromates vs. bromides
- Barbiturates
- Benzodiazepines (BZ)
- “Date-rape” drugs

Alcohols

Ethchlorvynol (Placidyl®)

Piperidinediones

Carbamates and bromides

Withdrawn sedative-hypnotics

New anxiolytics

Short-term anesthetics

Caffeine

Pharmacology

Sources: Plant-derived methylxanthines (caffeine, theophylline, theobromine); extracts of *Coffea arabica* (coffee), *Thea sinensis* (tea), *Cola acuminata* (cola).

Metabolic: Hepatic demethylation by CYP-450 to simpler methylxanthines.

Caffeinism: Syndrome of miosis, headache, tachycardia, palpitations, and delirium.

Physiology

Cardiovascular: Tachydysrhythmias, PVCs, cerebral vasoconstriction, hypertension, and increased cardiac output.

Gastrointestinal: Increased gastric acid and pepsin secretion, increased small intestine secretions.

Metabolic: Respiratory alkalosis, increased cAMP, reduced serum K and Ca leads to osteoporosis, increased muscle contractility, tremors, increased urinary catecholamines.

TABLE 9.1 Dependency Syndromes and Caffeine Doses

Dependency Syndromes

Nontoxic: increased alertness, decreased drowsiness and fatigue

Caffeinism: miosis, headache, tremors, palpitations, nervous irritability

Anxiety syndrome: hyperactivity, restless legs

Hypochondriasis syndrome: body discomfort, myalgias, chronic pain, fibromyalgia

Insomnia/headache syndrome

Depressive syndrome

Withdrawal syndrome: headache, nausea, yawning, rhinorrhea, drowsiness, lethargy, irritability

Caffeine Doses: mg/d (cups/d)

Nontoxic: 50–200 mg/d (1–2 cups)

Caffeinism: 200–500 mg/d (2–4 cups)

Anxiety: >500 mg/d (4–6 cups)

Hypochondriasis: 500–750 mg/d (>6 cups)

Insomnia: 500–750 mg/d (>6 cups)

Depressive: >750 mg/d (>6 cups)

Withdrawal: >235 mg/d (>2.5 cups)

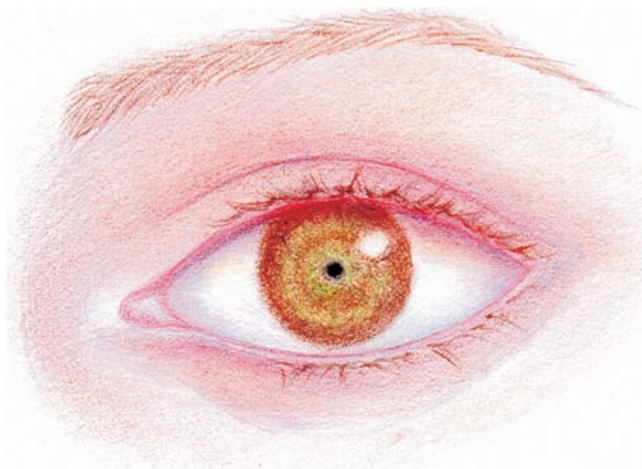


Figure 9.1 Miosis, Right Eye. Pupillary constriction or miosis characteristic of caffeine, cholinergic, ergotamine, opiod and phencyclidine (PCP) toxidromes.

Therapeutic Uses

- **Analgesic adjuvant:** Combined with APAP, ASA, and ibuprofen.
- **Migraine headaches:** Combined with ergots.
- **Diet, weight loss:** Combined with amphetamines and formerly PPA.
- Newborn apnea-bradycardia syndrome.

Toxicities

- Cardiovascular: SV and ventricular tachydysrhythmias, hypertension.
- Gastrointestinal: Increased gastric acidity leads to peptic ulcer, nausea and vomiting.
- Central nervous system (CNS): Agitation, restlessness, tremors, seizures.
- Metabolic: Reduced serum K and Ca (chronic osteoporosis = 2 cups/day, 100 mg/day).
- Muscle: Increased contractility, high creatine phosphokinase (CPK), rhabdomyolysis.

General Overdose Management

- Airway protection.
- Gastrointestinal decontamination: Early syrup of ipecac, activated charcoal (AC) and cathartic, consider multi-dose activated charcoal (MDAC) without additional cathartic.
- Hemoperfusion: As for all methylxanthines, including theophylline.

Specific Drug Therapy

- Anticonvulsants: Benzodiazepines (BZs) > barbiturates.
- Antidysrhythmics: Beta-blockers, calcium channel blockers (CCBs).
- Antiulcerogenics: H₂-blockers, proton (H)-pump inhibitors.
- Antiemetics: Ondansetron (5-HT-blocker) > metoclopramide (dopamine and 5-HT-blocker = chorea and dystonia possible side effects).
- Sedatives: BZs > barbiturates.

Ergotamines

Pharmacology

- Source: Plant alkaloids derived from the fungus, *Claviceps purpurea*, which contaminates rye and other grains.
- Metabolic: Poor gastrointestinal absorption, significant first-pass hepatic metabolism, volume of distribution (V_d) = 2 L/kg, half-life = 1.4–6.2 hours.
- Acute ergotism: Agitation, restlessness, nausea, vomiting, headache, delirium, fixed miosis, seizures, cerebral ischemia.
- Chronic ergotism: St. Anthony's fire = peripheral vasospasm-gangrene, burning extremities, purpura, angina, abortion.

Physiology

- CNS: Serotonin reuptake inhibitor.
- PNS: Alpha-agonist causing vasospasm in all vascular beds: cerebral > cardiovascular > mesenteric and renal > peripheral vasospasm.
- Cardiovascular: Hypertension with reflex bradycardia.
- Gastrointestinal: Centrally induced severe nausea and vomiting.

Therapeutic Uses

- Migraine: Ergotamine, ergotamine and caffeine (Cafegot®), methysergide (retroperitoneal fibrosis).
- Lactation inhibition: Bromocriptine.

- Uterine contraction: Ergonovine, methyl-ergonovine.

Ergotism

- Central effects: Agitation, headaches, hallucinations, cerebral ischemia, fixed miosis, seizures, facial twitching, nausea and vomiting.
- Peripheral effects: Hypertension and baroreceptor-mediated bradycardia.
- Ischemic effects: Angina then myocardial infarction, burning and gangrenous extremities (St. Anthony's fire), hemorrhagic vesiculations and bullae, mesenteric and renal infarction.

General Overdose Management

- Airway protection during seizures.
- Gastrointestinal decontamination: Syrup of ipecac and orogastric lavage often contraindicated due to severe vomiting, AC and sorbitol cathartic.
- Consider MDAC.

Specific Drug Therapy

- Cardiac, cerebral, mesenteric-renal ischemia: IV nitroglycerin (NTG), sodium nitroprusside, phentolamine.
- Mild peripheral vasospasm and ischemia: Orally prazosin, captopril, nifedipine (sublingual).
- CNS seizures and hallucinations: BZs.
- Hypercoagulability: Heparin, dextran, thrombolytics, clot extraction (chronic).

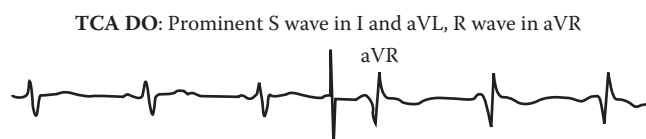


Figure 9.2 Electrocardiographic Evidence of Tricyclic Antidepressant Overdose. Electrocardiogram (ECG) tracing in a patient with a history of suicide attempt by tricyclic antidepressant (TCA) overdose that demonstrates widened QRS complexes indicative of cardiac sodium channel blockade that should correct with intravenous sodium bicarbonate administration. In addition, the ECG demonstrates a prominent S wave in Lead I and aVL and a prominent R wave in aVR, characteristic of TCA overdose.

TABLE 9.2 Antidepressants vs. Antipsychotics**Antidepressants**

Tricyclic and other cyclic antidepressants
Selective serotonin reuptake inhibitors (SSRIs)
Atypical antidepressants
Monoamine oxidase inhibitors (MAOIs)
Lithium

Antipsychotics (neuroleptics)

Phenothiazines
Thioxanthenes
Butyrophenones
New neuroleptics

Cyclic Antidepressants (CAs)

Epidemiology

CAs — First Generation

- 1987: 500,000 TCA overdoses/year.
- 1995: 12% of all intensive care unit (ICU) admissions were due to TCA overdose.
- Typical overdose: Female, age 20–29, single, employed, no history of drug abuse or prior suicide attempt.
- High case fatality rate (CFR): 70%.

SSRIs — Second Generation

- SSRIs have now surpassed TCAs as much safer frontline antidepressants with much lower CFRs.
- SSRIs have (1) no quinidine-like effects, which slow cardiac conduction and widen the QRS complex; (2) no alpha-blocking effects (orthostatic hypotension); and (3) no anticholinergic activity.
- SSRIs are epileptogenic only in large overdose.

Pharmacology

TCAs

- Cardiovascular: TCAs inhibit voltage-gated myocardial Na channels (quinidine-like effects) slowing conduction and prolonging QRS complex.
- CNS: Block histamine, dopamine, and muscarinic cholinergic receptors; inhibit reuptake of both norepinephrine (NE) and serotonin at adrenergic nerve terminals.
- Peripheral: α -Adrenergic blockers (orthostasis).
- Metabolism: Very large $V_d = 10\text{--}50\text{ L/kg}$, extensive first-pass hepatic metabolism, long half-life = 1–4 days, not dialyzable.

SSRIs

- CNS: Selectively inhibit serotonin reuptake, do not inhibit dopamine or norepinephrine reuptake, much safer profiles than TCAs.
- No quinidine-like effects.
- No anticholinergic effects.
- No alpha blockade.
- Metabolism: Large V_d , half-life = 1–6 days, not dialyzable.

First Generation vs. Second Generation

First generation (TCAs)

- General: Block both NE and serotonin reuptake, cause quinidine-like prolonged QRS complex, anticholinergic, α -blockers, and epileptogenic
- Examples:
 - Amitriptyline (Elavil®)
 - Clomipramine (Anafranil®)
 - Desipramine (Norpramin®)
 - Doxepin (Sinequan®)
 - Imipramine (Tofranil®)
 - Nortriptyline (Pamelor®)

Second generation (SSRIs, etc.)

- General: Not Na-channel blockers, not anticholinergics, not α -blockers, rarely epileptogenic
- Example SSRIs: Fluoxetine (Prozac®)
- Paroxetine (Paxil®), Sertraline (Zoloft®)
- Example SSRI and alpha-blocker: Trazodone (Desyrel®)
- Example SSRI and NE/dopamine reuptake inhibitor: Venlafaxine (Effexor®)
- Example NE/dopamine reuptake inhibitor: Bupropion (Wellbutrin®, Zyban®)

Toxicity

TCA's

- Cardiac: Quinidine-like (IA) effects = block cardiac Na channels, reduced conduction and prolong QRS; anticholinergic effects = tachydysrhythmias; direct myocardial depression due to Na and K channel blockade.
- CNS: NE and dopamine reuptake inhibitor, agitation, hallucinations, confusion, sedation, coma, seizures, central and peripheral anticholinergic effects.
- Peripheral vascular: α -Adrenergic blockers = hypotension.
- Serotonin syndrome: Clomipramine only.

SSRIs

- Cardiovascular: No cardiotoxicity or alpha blockade.
- CNS: Jitteriness, dizziness, blurred vision, depressed mental status, and rarely seizures.
- Gastrointestinal: Anorexia, nausea and vomiting.
- Serotonin syndrome: All SSRIs can cause the serotonin syndrome.

SSRIs vs. Neuroleptics

Serotonin Syndrome

- Definition: An acute idiosyncratic reaction due to hyperstimulation of central serotonin receptors by increased synaptic serotonin levels; characterized by agitation, mental status changes, diaphoresis, tremor, rigidity, myoclonus, hyperreflexia, incoordination, and seizures.
- Etiology: (1) 5-HT breakdown inhibitors — MAOIs; (2) 5-HT RIs — SSRIs and tramadol; (3) 5-HT agonists or precursors — lithium and buspirone; (4) 5-HT releasers — MDMA (Ecstasy), meperidine, and dextromethorphan.
- Treatment: External cooling, muscle relaxants — BZs and NMBs; self-limited and resolves within 4 hours.

Neuroleptic Malignant Syndrome

- Definition: A subacute idiosyncratic reaction that develops during early tx with neuroleptics from three classes (phenothiazines, thioxanthenes, butyrophenones); characterized by mental status changes, hyperthermia, muscular

hypertonicity and lead-pipe hyperreflexia, tremors, akinesia and choreoathetosis.

- Etiology: Central dopamine receptor blockade with severe extrapyramidal reactions ranging from dystonia to lead-pipe rigidity and choreoathetosis.
- Treatment: DC neuroleptics, cool in ice, BZs, consider dantrolene; usually occurs within first week of treatment — if neuroleptics indicated, select one from another class.

Diagnosis and Management

TCA's

- Diagnosis: ECG-increased QT, QRS > 100 msec, sinus tachycardia, R wave — aVR; serum levels > 1000 ng/mL.
- Initial management: No ipecac due to seizures; orogastric lavage; AC, 1 g/kg and sorbitol, second dose AC — no cathartic.
- Specific management: Na and hypervent low TCA binding to Na channels; NaHCO_3 1–2 mEq/kg bolus, then 3 amp/L D_5W infusion every 4–6 hours = art pH 7.50–7.55. Seizures: IV BZs. Hypotension: LR-NS load, direct vasopressors (NE), dopamine contraindicated due to vasodilation.

SSRIs

- Diagnosis: Clinical = nausea, vomiting, dizziness, blurred vision, tachycardia, rarely seizures in massive overdose. No specific ECG changes.
- Treatment: Ipecac contraindicated due to mental status depression and low risk of seizures; dextrose and thiamine bolus; oral AC, 1 g/kg and sorbitol, 1 g/kg; consider MDAC for co-ingestions. SSRI overdoses are rarely life-threatening, unless there are co-ingestions.

Monoamine Oxidase Inhibitors

Pharmacology

- Mechanism: A class of ADs that inhibit both hepatic (gastrointestinal) MAO-A and CNS MAO-B to cause mood elevation by an increase in all CNS monoamines: NE, epinephrine, Dopamine and 5-HT (Serotonin).
- Types (all orally): (1) Old irreversible MAOIs = phenelzine, tranylcypromine, selegiline (anti-Parkinson drug); and (2) new reversible MAOIs.

Toxicity

- Mechanism: Increased norepinephrine and epinephrine effects = tachycardia and hypertension, headache, angina, myocardial infarction (MI), cerebrovascular accident (CVA), cardiovascular collapse. Increased 5-HT and Dopamine effects = agitation, delirium, obtundation, nystagmus, hyperreflexia, tremors, myoclonus, muscle rigidity, hyperthermia, diaphoresis, seizures, respiratory depression.
- Interactions: (1) Drug interactions: all sympathomimetic drugs, SSRIs, cocaine some opioids (codeine, meperidine, and dextromethorphan); (2) foods high in tyramine = aged cheeses, red wines, pickled or smoked meats and fish.

MAOIs and Amines

Safe = Direct-Acting Sympathomimetics

- Epinephrine
- Norepinephrine
- Isoproterenol
- Methoxamine
- Phenylephrine

Unsafe = Indirect-Acting and Combined Sympathomimetics

- Indirect-acting:
 - Amphetamines
 - Phenylpropanolamine
 - Fenfluramine
 - Phentermine
 - Tyramine
- Combined direct-indirect:
 - Dopamine
 - Metaraminol
 - Ephedrine
 - Mephentermine

TABLE 9.3 MAOIs and Drugs

Interacting Drugs	Manifestations of Interactions
Indirect sympathomimetics	Hypertensive crisis and death
L-dopa and tryptophan	Hypertension, not deadly
Antidepressants (TCAs, SSRIs)	Disorientation, seizures, death
Opioids (meperidine, dextromethorphan)	Hyperthermia, death
Cocaine	Hyperthermia, death
Theophylline > caffeine	Hyperthermia, potentially deadly
Codeine and barbiturates	Sedation potentiation
Hypoglycemic agents	Hypoglycemia potentiation

MAOIs and Foods

Foods to Avoid

- High tyramine foods:
 - Aged cheeses
 - Red wines
 - Yeast
 - Smoked and pickled meats and fish

Foods to Beware of and Safe Foods

- Beware: moderate tyramine:
 - Avocados
 - Beer
 - Meat extracts
- Low tyramine safe foods:
 - Cottage and cream cheeses
 - Chocolate and caffeine
 - Distilled alcohols
 - Fruits
 - Soy sauce
 - Yogurt and sour cream

Diagnosis

- Delayed onset: Consistently delayed (12 hours) onset of symptoms or few symptoms post overdose.
- Early symptoms: NE/Epi = tachycardia, hypertension, headache; 5-HT and Dopa = agitation, delirium, obtundation, nystagmus, tremors, and hyperthermia.
- Late symptoms: NE/Epi = angina, MI, CVA; 5-HT and Dopa = muscular rigidity, seizures, rhabdomyolysis, myoglobinuria, renal failure, DIC, and ARDS.

Management

- General: Syrup of ipecac contraindicated due to seizures; orogastric lavage and AC; seizure control and muscle relaxation with benzodiazepines; aggressive cooling for hyperthermia.
- Specific: For hypertension, use short-acting vasodilators (SCN); and for hypotension, use only direct-acting vasopressors (NE and phenylephrine). Bretylium is contraindicated due to its initial release of NE.

Neuroleptics

Classification

First Generation (All Cause NMS)

- Phenothiazines:
 - Chlorpromazine (Thorazine®)
 - Prochlorperazine (Compazine®)
 - Fluphenazine (Prolixin®)
- Thioxanthenes:
 - Thiothixine (Navane®)
- Butyrophenones:
 - Droperidol (Inapsine®)
 - Haloperidol (Haldol®)

Second Generation (No NMS, except Loxipine)

- Indoles
- Dibenzoxapines
- Loxipine (Loxitane)
- Dibenzodiazepines
- Diphenylbutylpiperidines
- Benzisoxazoles
- Risperidone (Risperdal®)

Pharmacology

Mechanisms of Action

- Dopamine receptor blockade peripherally and centrally within the limbic system
- Alpha-adrenergic blockade
- Central and peripheral cholinergic blockade
- Serotonin reuptake inhibition centrally

Metabolism and Major Side Effects

- Extensive hepatic metabolism to active metabolites, increased half-life.
- Acute dopamine inhibition = parkinsonism syndrome of extrapyramidal effects, treatment = anticholinergics (Benzotropin [Cogentin®] and trihexyphenidyl [Artane®]) or antihistamines (diphenhydramine [Benadryl®]).

- Chronic dopamine receptor blockade causing increased synaptic dopamine = tardive dyskinesias.
- Neuroleptic malignant syndrome = increased T and EPS.

Toxicology

Toxicities

- Cardiovascular: Quinidine-like effects = prolonged QT, PR, and QRS complex; direct myocardial depression; alpha blockade with orthostasis.
- CNS: Anticholinergic and antidopaminergic = parkinsonism, rabbit syndrome, tardive dyskinesia.
- Gastrointestinal: Anticholinergic = decreased secretions and gastrointestinal motility, leads to pseudo-obstruction from concretions.
- GU: Priapism, urinary retention.

Adverse Effects

- Acute dystonia: Oculogyric crisis, torticollis, opisthotonos.
- Akathisia: Restlessness.
- Parkinsonism: Classical and rabbit syndrome = perioral tremors.
- Neuroleptic malignant syndrome: Lead-pipe rigidity, hyperthermia, choreoathetosis.
- Tardive dyskinesia: Choreoathetosis without hyperthermia and rigidity.

Overdose

Diagnosis and General Management

- Diagnosis: Positive urine ferric chloride test; radiopaque phenothiazine concretions on abdominal x-ray; serum levels unhelpful.

- General management: Orogastric lavage > ipecac emesis due to CNS effects; consider MDAC; HP and HD useless due to increased VD; cardiovascular support with α -agonists only, as β -agonists cause vasodilation; NaHCO_3 for conduction block and prolonged QRS complex; physostigmine for central anticholinergic syndrome could exacerbate conduction blockade.

Specific Syndrome Management

- Acute dystonia: Mechanism = unknown; treatment = diphenhydramine, BZs.
- Akathisia: Mechanism = unknown; treatment = same at reduced doses.
- Parkinsonism: Mechanism = dopamine antagonism; treatment = anticholinergics at low doses.
- NMS: Mechanism = dopamine antagonism; treatment = cooling, BZs, consider dantrolene.
- Tardive dyskinesias: Mechanism = excess dopamine activity; treatment = consider physostigmine.

Lithium

History

- An early “picker-upper” and ingredient of Seven-Up®.
- Lightest metal known that behaves like its periodic table neighbors, Na and K.
- A salt substitute for hypertensives prior to antihypertensives.
- Exhibits a very narrow therapeutic:toxic ratio.
- Uses: Bipolar disorders and cluster headaches.

Pharmacology

- Li is rapidly absorbed and peaks in serum within hours.
- Therapeutic level = 0.6–1.2 mEq/L; acute toxicity >4.0 mEq/L (HD indicated); chronic toxicity >1.5 mEq/L.
- Low V_d , no protein binding, not metabolized, 90% renally excreted, and easily dialyzable.
- Mechanism unknown.
- Primary toxicity neurologic: Mental status depression, tremor, clonus, choreoathetosis, seizures, coma, parkinsonism (chronic toxicity).

Toxicity

Acute Li toxicity

- Action level: >4.0 mEq/L.
- CNS > Gastrointestinal > cardiovascular:
 - CNS: Mild-lightheadedness and tremor; moderate drowsiness, tinnitus, muscle twitching, hyperreflexia; severe clonus, choreoathetosis, seizure, coma.
 - Gastrointestinal: Nausea and vomiting.
 - Cardiovascular: Prolonged QT, ST, T wave changes.
- Renal, endocrine, Dermal: None.

Chronic Li toxicity

- Action level: >1.5 mEq/L
- CNS > renal > endocrine:
 - CNS: Mild = same; moderate = same; severe = memory loss, psychosis, parkinsonism.
 - Gastrointestinal: None.
 - Cardiovascular: Myocarditis.
 - Renal: Interstitial nephritis, diabetes insipidus, renal failure.
 - Endocrine: Hypothyroidism, cretinism.
 - Dermal: Edema, dermatitis, ulcers.

Overdose

- Ipecac contraindicated due to prominent neurotoxicity.
- Orogastric lavage for retained pills.
- Li is not adsorbed to AC. AC is contraindicated unless there is co-ingestion.
- Volume (NS) hydration to promote diuresis and renal excretion.
- WBI with PEG-ELS for sustained-release lithium (Lithobid®).

Enhanced elimination

- Peritoneal dialysis is contraindicated.
- Hemodialysis is best, especially for high Li levels (>4.0 mEq/L) and patients with CHF, pulmonary edema, or CRF. Li rebound occurs post-dialysis.
- CAVH and CVVH are both good for slow Li removal in mild-moderate overdoses without rebound high [Li] with HD.

Anticonvulsants

Classification

- Prolonged Na-channel inactivators:
 - Carbamazepine
 - Tegretol®
 - Phenytoin (Dilantin®)
- GABA enhancers:
 - Barbiturates
 - Benzodiazepines
 - Gabapentin (Neurontin®)
 - Vigabatrin
- Na channel blockers and GABA enhancers
 - Felbamate
 - Lamotrigine
 - Valproic acid

Sodium Channel Blockers

Carbamazepine

- Acute toxicity: CNS > cardiovascular:
 - CNS: Ataxia, dysarthria, dystonia, clonus, choreoathetosis, seizures, stupor.
 - Cardiovascular: Prolongs QT, widens QRS, torsades de pointes, VT.
- Chronic toxicity: Headache, diplopia, ataxia.
- Side effects: Aplastic anemia, Stevens-Johnson syndrome.
- Treatment: AC, MDAC, abdominal x-ray for concretions, NaHCO_3 for wide QRS, BZs for seizures, hemodialysis ineffective.

Phenytoin

- Acute toxicity: CNS > Gastrointestinal > endocrine > cardiovascular:
 - CNS: Ataxia, nystagmus, ophthalmoplegia, dysarthria, hyperreflexia, depressed mental status, hallucinations, rarely seizures, no ECG changes (Class IB antidysrhythmic) and hypotension.
- Chronic toxicity: Megaloblastic anemia, aplastic anemia, hypothyroidism, teratogenicity.

- Side effects: Nausea, vomiting, gingival hyperplasia.
- Treatment: AC, MDAC, BZs for seizures, HD and HP ineffective.

GABA Inhibition Enhancers

Gabapentin

- Acute toxicity: CNS > gastrointestinal; very safe due to lack of protein binding, no metabolic biotransformation, and 100% renal excretion.
 - CNS: Somnolence, sedation, dizziness, ataxia.
- Treatment: AC, all symptoms will resolve in 48 hours.

Vigabatrin

- Acute toxicity: CNS only, similar to gabapentin.
 - CNS: Acute psychosis.
- Chronic toxicity: Psychosis.
- Treatment: Supportive.

Combined Sodium Channel Blockers and GABA Enhancers

Felbamate

- Acute toxicity: Mild gastrointestinal symptoms.
- Chronic toxicity: psychosis.
- Side effects: Nausea, vomiting, pancreatitis, fulminant hepatic failure (20%), aplastic anemia.
- Treatment: AC.

Lamotrigine

- Acute toxicity: CNS > cardiovascular:
 - CNS: Ataxia, nystagmus.
 - Cardiovascular: Prolongs QRS complex.

- Chronic toxicity: Nausea, headache, blurred vision, diplopia, dizziness, ataxia.
- Side effects: Stevens-Johnson syndrome, toxic epidermal necrolysis.

Valproic Acid

- Acute toxicity: Produces hepatotoxic metabolites.
- CNS: Lethargy, cerebral edema due to hyperammonemia from metabolite that inhibits NH_3 metabolism.
- Gastrointestinal: High LFTs and high NH_3 .
- Hemetologic: Low white blood cells and platelets.
- Side effects: Sedation, ataxia, tremor, Reye's-like fulminant hepatitis.
- Treatment: AC, MDAC, carnitine for high NH_3 , HD and HP ineffective.

Sedative-Hypnotics

Definitions

- Sedatives: Drugs that reduce activity, moderate excitement, and exert a calming effect.
- Hypnotics: Drugs that produce drowsiness and facilitate sleep.
- Anxiolytics: Sedative-hypnotics that also have anti-anxiety properties (e.g., BZs, zolpidem, and buspirone).

Classification

- Barbiturates: Ultra-short acting, short acting, intermediate acting, long acting.
- Non-barbiturates: BZs, alcohols, piperidinediones, paraldehyde, meprobamate, new anxiolytics-zolpidem, buspirone.

Mechanism

- Barbiturates and BZs: Enhance inhibitory GABA-mediated chloride currents in CNS by binding at different receptor sites on the GABA receptor-Cl ionophore complex.
- Barbiturates and BZs: Potentiate each other's sedative, hypnotic, and anticonvulsant effects.
- BZs also exert muscle relaxant effects centrally and peripherally.
- Antidote for BZs: Flumazenil, a pure BZ-receptor antagonist.

Pharmacology

- SHs induce sleep by reducing time to sleep onset, reducing REM sleep, increasing stage 2 non-REM sleep. In overdose, SHs depress CNS to stage III anesthesia.
- Tolerance to sedation in 1 week.
- Barbiturates and BZs are rapidly absorbed in SI; as their lipid solubility increases, blood-brain barrier penetration increases, and CNS depression increases.

- Lipid-soluble barbiturates and BZs are highly protein bound, poorly filtered renally, and not dialyzable. BZs are hepatically biotransformed to active metabolites (oxazepam); barb met yields few active intermediates.

Diagnosis

Physical Findings

- CNS: Mydriasis, mild-mod ataxia, slurred speech, incoordination leads to increased CNS depression, stupor, coma; rarely euphoria-excitation (methaqualone), toxic psychosis (triazolam, flurazepam, glutethimide), and extrapyramidal effects (methaqualone).
- Cardiovascular: Myocardial depression due to hypotension and heart rate and smooth muscle vasodilation; rarely AT and SVT (alcohols, chloral hydrate, meprobamate).
- Pulmonary: Respiratory depression and arrest.
- Metabolic: Hypothermia (barbiturates, BZs, and bromides).

Lab and X-ray Findings

- Labs — to rule out other causes of stupor and coma (especially metabolic and neurologic causes): Electrolytes, BUN, creatinine, glucose, serum alcohol and phenobarbital, LFTs, ABGs.
- Abdominal x-ray: Gastric concretions with barbiturates and meprobamate.
- Endoscopy: To break up and/or remove concretions.

Pathognomonic Signs

- Breath odor: Chloral hydrate and paraldehyde = pear-like; ethchlorvynol (Placidyl®) = pungent plastic or vinyl smell.
- Skin: (1) Barbiturate (6.0–6.5 %) (and ethchlorvynol) blisters = bullous lesions on hands, buttocks, knees; (2) bromoderma = bromide acne =

ulcerating acneiform eruption starts on face and spreads over body.

- Gastrointestinal: Hemorrhagic gastritis unique to chloral hydrate overdose.

Overdose Management

Basic Management

- Airway protection: ETT.
- Orogastric lavage: Reduced gastric motility and concretion potential.
- Initial AC slurry: 1 g/kg and cathartic.
- MDAC: q 2–4 h, 0.5 g/kg, no additional cathartic, especially for phenobarbital, meprobamate, and glutethimide.
- WBI-PEG/ELS: For gastrointestinal concretions on x-ray (meprobamate) and overdoses with sustained-release SHs (diazepam CR).

Enhanced Elimination

- Acid-base manipulation: Urinary alkalization only for phenobarbital ($pK_a = 7.21$), NaHCO_3 1–2 mEq/kg iv bolus, then 150 mEq/L D_5W to keep arterial pH 7.45–7.50 and urine pH 7.5–8.0; replace K losses.
- Hemoperfusion: Preferred over HD for all SH overdoses, except bromides (HD only); due to low V_d , increased lipid solubility, increased water solubility, increased protein binding. HP very effective for phenobarbital and meprobamate.
- Antidote: Flumazenil for all BZs and zolpidem, can precipitate BZ-withdrawal reactions.

Bromates vs. Bromides

Bromates

- Use: Hair neutralizers and straighteners, bread preservatives.
- Toxicity: Like aminoglycosides, bromates target the hair cells of the cochlea and the renal tubules impairing their unique abilities to regulate electrochemical gradients. Bromate ototoxicity is permanent, but renal failure is reversible.
- Treatment: Lavage and AC.

Bromides

- Use: Old nerve-headache tonics and sedatives (Bromo-Seltzer®); gas fumigant for soil, fruits and vegetables; vehicle for some drugs (bromopheniramine and dextromethorphan).
- Toxicity: Severe gastrointestinal mucosal irritant, brown-stained tongue, progressive CNS depression = Bromism: headache, apathy, irritability leads to confusion, ataxia, tremor, dysarthria, psychosis leads to coma. Later Bromoderma = like ioderma with ulcerating facial acne; treatment = antibiotics and Retin-A®.
- Treatment: Lavage and AC, hemodialysis.
- Bromoderma acne resembles ioderma acne, with weeping and ulcerating facial pustules and indicates long-term exposure to brominated or iodinated products.

Barbiturates

Barbiturate Classification

- Ultra-short acting (redistribution, then hepatic elimination): Methohexital, thiamylal, thiopental.
- Short acting (hepatic > renal): Hexobarbital, pentobarbital, secobarbital.
- Intermediate acting (hepatic > renal): Amobarbital, aprobarbital, butabarbital.
- Long acting (mostly renal elimination): Barbitol, phenobarbital, primidone.

Barbiturate Pharmacology

Short and Intermediate Acting

- High pK_a , very alkaline
- More lipid soluble
- More protein bound
- Rapid onset, short duration
- Almost completely metabolized hepatically
- Alkaline diuresis ineffective
- Enhanced elimination by hemoperfusion only

Long acting

- Lower pK_a , weak acids
- Less lipid soluble
- Less protein bound

- Slow onset, long duration
- Almost completely renally eliminated
- Enhanced elimination by MDAC, alkaline diuresis, and hemoperfusion > hemodialysis

Barbiturate Toxicity

- CNS: Slurred speech, ataxia, lethargy, confusion, headache progressing to anesthesia, coma, respiratory arrest, cerebral edema.
- Cardiovascular: Direct myocardial depression, peripheral vasodilation, pulmonary edema, cardiac arrest.
- Dermal: Barbiturate blisters = cutaneous bullae (6.5%).
- Metabolic: Hypothermia.
- Miscellaneous: CYP-450 inducers, increase δ -ALA and contraindicated in porphyrias.

Drug–Drug Interactions

- Hepatic enzyme induction: Increased metabolism of drugs.
- Synergistic CNS depression: With other SHs and all CNS depressants (especially alcohol).
- Increased production of δ -ALA: Contraindicated in porphyrias.
- ASA and warfarin: Displace barbiturates from their protein binding sites.

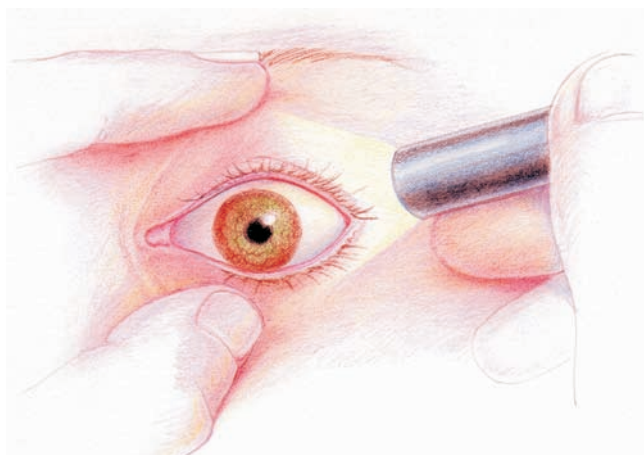


Figure 9.3 Mydriasis, Right Eye. Pupillary dilation or mydriasis characteristic of an anticholinergic toxidrome and overdoses with alcohol and barbiturates.

Benzodiazepines (BZ)

BZ Classification

Short Acting (Half-life < 24 hours)

- Alprazolam (Xanax®)
- Flurazepam (Dalmane®)
- Lorazepam (Ativan®)
- Midazolam (Versed®)
- Temazepam (Restoril®)
- Triazolam (Halcion®)
- Flunitrazepam (Rohypnol®, date-rape, not FDA-approved)

Long Acting (Half-life > 24 hours)

- Chlordiazepoxide (Librium®)
- Clonazepam (Klonopin®) — only BZ used as a chronic anticonvulsant
- Diazepam (Valium®)
- Oxazepam (Serax®)

BZ Toxicity

- General: Weakness, nausea, diarrhea, chest pain.
- CNS: Headache, vertigo, blurred vision, obtundation, stupor, coma — all potentiated by co-ingestions, especially with alcohol.
- Cardiovascular: VS well-maintained, not arrhythmogenic.
- Tolerance: Occurs rapidly, within 1 week.
- Withdrawal: Headache, tremor, weight loss, paresthesias, perceptual losses.

Miscellaneous and Drug–Drug Interactions

- Miscellaneous: Triazolam (Halcion®) = toxic psychosis; flurazepam (Dalmane®) = nightmares and hallucinations.
- Synergistic CNS depression: Potentiate the actions of all other CNS depressants.
- Cimetidine: Inhibits hepatic microsomal enzymes and increased half-lives of all BZs, especially those with active metabolites (oxazepam).

“Date-Rape” Drugs

- Gamma-hydroxybutyrate (GHB, gamma-hydroxybutyric acid) and its precursors: gamma-butyrolactone (GBL) and 1, 4-butanediol.
- Flunitrazepam (Rohypnol®).
- “Date-Rape”: GHB.

Toxicology

Street names: Liquid Ecstasy, Easy Lay.

- GABA metabolite: A naturally occurring CNS (brain) metabolite of GABA, the inhibitory neurotransmitter.
- Rapid oral absorption: Peak onset in 15 minutes; duration 1.5–2 hours.

Clinical Manifestations

- CNS: Initial relaxation, tranquility, disinhibition; followed rapidly by loss of consciousness, delirium, amnesia; rarely seizures.
- Cardiopulmonary: Bradycardia, mild hypotension, transient respiratory depression.
- Gastrointestinal: Vomiting.

Use/Abuse and Management

Methods of Use and Abuse

- Licit use: Narcolepsy, not FDA-approved in the United States.
- Ineffective use: By body builders to promote rest, fasting, fat metabolism, muscle mass and high growth hormone levels.
- Illicit use: “Date-rape.”

General Management of Overdose

- Airway protection: Monitor oxygenation and ventilation.
- Consider coma cocktail with thiamine and D₅₀W; Flumazenil and naloxone ineffective.
- Atropine: For bradycardia.
- Consider physostigmine.

Flunitrazepam

Toxicokinetics

- Rohypnol®: Foreign trade name, U.S. street drug.

- Short-acting benzodiazepine: 7–10 times as potent as diazepam.
- Rapid oral absorption: Peak onset in 15–20 minutes; duration 4–6 hours.

Clinical Manifestations and Management

- Profound CNS depression with maintenance of stable VS.
- Anterograde amnesia common.
- General overdose management: Supportive, protect airway, monitor oxygenation and ventilation.
- Antidote: Flumazenil.

Alcohols

Chloral Hydrate (Noctec®)

- Pharmacology: Severe gastrointestinal irritant, rapidly absorbed, first-pass active metabolite = trichloroethanol; “Mickey Finn” = chloral hydrate and ethanol.
- CNS: Mimics barbiturate overdose with stupor and coma; pathognomonic pear-like breath odor.
- Gastrointestinal: Nausea, vomiting, hemorrhagic gastritis with gastric and SI necrosis and gastrointestinal perforation; esophageal stricture.
- Cardiovascular: Myocardial sensitization leads to depression, ventricular arrhythmias = VT, VF, torsades. Treatment: β -blockers.
- Miscellaneous: Genotoxic, animal carcinogen.

Ethchlorvynol (Placidyl®)

- Pharmacology: Rapidly absorbed, 90% hepatically metabolized.
- CNS: Central respiratory depression, stupor progressing to prolonged deep coma; pathognomonic plastic- or vinyl-smelling breath.
- Cardiovascular: Myocardial depression = hypotension and bradycardia.
- Pulmonary: Respiratory depression, pulmonary edema, especially after IV overdose.
- Dermal: “Barbiturate blisters” on hands, knees, and buttocks.
- Treatment: Hemoperfusion.

Piperidinediones

Glutethimide (Doriden®)

- Acute overdose: Similar to barbiturate overdose, profound and prolonged coma like ethchlorvynol, sudden apnea, and seizures.
- Chronic overdose: Toxic psychosis, ataxia, seizures, peripheral neuropathy.
- Miscellaneous: Anticholinergic, thick bronchial secretions block major airways.

Methypylon (Noludar®)

- Overdose: Stupor, coma, hypotension, pulmonary edema, shock.
- Miscellaneous: Cytochrome P-450 inducer, increases δ -ALA synthetase and contraindicated in porphyrias.

Carbamates and Bromides

Meprobamate (Miltown®)

- Overdose: Can cause euphoria, seizures, coma, hypotension, respiratory depression, pulmonary edema, arrhythmias.
- Miscellaneous: Forms large masses or bezoars of pills that can become concretions.
- Treatment: Lavage and endoscopy to remove concretions, WBI with PEG-ELS if concretions detected in gastrointestinal tract on abdominal x-ray.

Bromides

- Overdose: Old nerve tonics (Bromo-seltzer) and nematocidal fumigants; very irritating to the gastrointestinal tract = increased vomiting; increased sedation leads to stupor and coma; bizarre neurologic and psychologic effects (bromism).
- Bromism: Bizarre behavior, delusions, hallucinations, headache, apathy, irritability, confusion, dysarthria, tremors, ataxia, anorexia-weight loss, bromoderma.
- Miscellaneous: Spurious hyperchloridemia.

Withdrawn Sedatives-Hypnotics

Methaqualone (Quaalude®)

- Overdose: CNS = euphoria (cause for abuse), fatigue, delirium, hypertonia, myoclonus, hyperreflexia, stupor-coma, respiratory arrest.
- Miscellaneous: Withdrawal syndrome with agitation, delirium, seizures.

Paraldehyde (Paral®)

- Overdose: An alcohol metabolite, overdose mimics ethanol intoxication, pear-smelling breath; formerly used to cover ethanol detoxification; causes a high anion gap metabolic acidosis.
- Anion gap = $\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-) = 12 \pm 4 \text{ mEq/L} = 8-16 \text{ mEq/L}$.
- MUDPPILES: Methanol, Uremia, Diabetic ketoacidosis, Paraldehyde, Phenformin, INH, Iron, Lactic acidosis, Ethylene glycol, Salicylates.

New Anxiolytics

Buspirone (Buspar®)

- Pharmacology: Central serotonin and dopamine reuptake inhibitor.
- Overdose: Gastrointestinal symptoms, drowsiness, dizziness, miosis, rarely dysphoria and extrapyramidal reactions, no cardiovascular and respiratory depressant effects.

Zolpidem (Ambien®)

- Pharmacology: A non-BZ that has its own unique BZ receptor binding sites; unlike BZs, has little effect on the stages of sleep.
- Overdose: Drowsiness, sensory distortion, psychotic reactions, rarely respiratory depression and coma; high CFR with co-ingestions (alcohol, SSRIs).
- Antidote: Flumazenil.

Short-Term Anesthetics

Propofol (Diprivan®)

- Pharmacology: GABA enhancer.
- Overdose: Transient apnea, dose-related respiratory depression and hypotension, not arrhythmogenic.

- Miscellaneous: Lipemic serum due to high TGs; histamine and anaphylactoid reactions to soy-bean-egg emulsion formulation, rarely true anaphylaxis; supports bacterial overgrowth.

Etomidate (Amidate®)

- Pharmacology: GABA enhancer.
- Overdose: Same as propofol and involuntary muscle movements, rarely severe cardiovascular and respiratory depression.
- Miscellaneous: Suppresses adrenal steroid hormone production — cortisol and aldosterone; no longer recommended for prolonged ICU sedation.

Illicit Substances: Outline

Cocaine

- History
- Epidemiology
- Pharmacology
- Toxicology
- Methods of abuse
- Clinical manifestations
- General overdose management
- Specific overdose management
- Management: body packers vs. stuffers

Amphetamines

- Pharmacology
- Abuse
- Prescription v. designer
- Acute vs. chronic amphetamine toxicity
- Overdose management

Phencyclidine (PCP)

- History of PCP
- Pharmacology of PCP
- Clinical manifestations
- Lab findings
- Management of PCP overdose

Lysergic acid diethylamide (LSD)

- Common hallucinogens
- LSD Pharmacology
- Clinical manifestations
- LSD intoxication

Marijuana

- Epidemiology
- Pharmacology
- Acute vs. chronic marijuana toxicity
- Management of marijuana intoxication

“Date-rape” drugs

- “Date-rape”: GHB
- Flunitrazepam
- Miscellaneous date-rape drugs

Cocaine

History

- Cocaine is a natural plant alkaloid of the Central and South American cocoa plant.
- Peruvian Incas first used cocaine-filled saliva as a local anesthetic for ritual and war wound trephinations.
- Cocaine was an early ingredient of Coca-Cola.

Epidemiology

- Cocaine abuse is the most frequent drug-related cause of emergency department visits in the United States.
- More than 25 million Americans have tried cocaine at least once.
- More than 5 million Americans use cocaine one or more times a month.

Pharmacology

- Ester-type LA: Rapid onset = inhalation: onset 1–3 minutes and peaks 20–30 minutes; IV: onset within seconds and peaks 3–5 minutes.
- Three routes of metabolism: (1) hydrolysis by plasma pseudocholinesterases to ecgonine methyl ester (EME), major metabolite (50%); (2) nonenzymatic hydrolysis to longest active metabolite, benzoylecgonine (40%, used as the preferred cocaine urine drug screen marker due to its long half-life); (3) hepatic N-demethylation to norcocaine (10%).

Toxicology

- Pseudocholinesterase deficiency: Predisposes to high toxicity due to hereditary ineffectiveness of cocaine's primary metabolic pathway via plasma pseudocholinesterases.
- LA effect (IB): Produced by Na channel blockade centrally, peripherally, and in the myocar-

dium, a quinidine (Type IA antiarrhythmic) effect.

- Vasoconstriction: Results from catecholamine reuptake inhibition with intense cerebral, coronary, and mesenteric vasoconstriction.
- Rostral-caudal CNS stimulation: Euphoria, excitement, restlessness, hyperthermia, tonic-clonic seizures, all resulting from reuptake inhibition.
- Alcohol and cocaine: Results in the hepatic formation of a long-acting, more cardiotoxic metabolite — coca-ethylene.

Methods of Abuse

- Snorting: Nasally insufflated; using “head shop” paraphernalia = spoons, dollar bills, and straws.
- Free-basing: Home conversion of hydrochloride salt to pure cocaine base for inhalation or IV use by flame processing in volatile solvents (ether, benzene, alcohol) (e.g., Richard Pryor).
- Crack: A highly purified and dry-processed smokeable form of cocaine, available in small, inexpensive packages of “chips” or “rocks.”

Clinical Manifestations

- Hyperthermia: Resulting from serotonin-induced high psychomotor hyperactivity and low heat dissipation from peripheral vasoconstriction.
- CNS: Mydriasis, seizures, greater risk of cerebrovascular accidents (CVAs) = subarachnoid hemorrhage, intracranial hemorrhage, transient ischemic attacks.
- Acute cardiovascular: Tachycardia, hypertension, tachyarrhythmias, myocardial infarction (MI), vascular endothelial damage and platelet aggregation and adhesion, subacute bacterial endocarditis (SBE) from septic emboli.
- Chronic cardiovascular: Coronary artery disease (CAD) and left ventricular hypertrophy

(LVH) = dilated cardiomyopathy, peripheral vascular disease, and acute aortic dissection.

- Pulmonary: Pneumomediastinum from deep inhalation with breath-holding, noncardiogenic pulmonary edema (NCPE) may result from adrenergic tone, pulmonary capillary leak, and pulmonary hypertension.
- Skeletal muscle: Muscular hyperactivity and rigidity leading to muscle damage, high creatine phosphokinase (CPK) levels, rhabdomyolysis; myoglobinuria may lead to acute tubular necrosis (ATN) and acute renal failure (ARF).
- Gastrointestinal vasoconstriction: Gut ischemia and mesenteric thrombosis may lead to bowel necrosis with pneumatosis intestinalis.
- Uteroplacental and fetal: Spontaneous abortion, abruptio placenta, intrauterine growth retardation (IUGR), limb autoamputation, microcephaly, and low birth weight.

Differential Diagnosis of Sympathetic Toxidromes

- Toxins: Cocaine, phenycyclidine (PCP), amphetamines, caffeine, hallucinogens, phenylpropanolamine (PPA), theophylline, ephedrine, pseudoephedrine, tyramine, monoamine oxidase inhibitors (MAOIs).
- Metabolic: Thyrotoxicosis, pheochromocytoma, hypoglycemia, serotonin syndrome, neuroleptic malignant syndrome.
- Withdrawal: Ethanol, sedative-hypnotics.
- Neuropsychiatric: Status epilepticus, mania, psychosis, schizophrenia.

Diagnostic Tests

- Labs: Hyperglycemia, hypokalemia, increased CPK, and increased CPK-MB.
- Electrocardiogram (ECG): All tachyarrhythmias increased, ischemia, MI.
- Head CT: All CVAs increased = subarachnoid hemorrhage (SAH), intracranial (ICH), interventricular hemorrhage (IVH), ischemic cerebral infarcts, septic cerebral emboli, brain abscesses.
- Abdominal x-rays: Body packing mules vs. body stuffers; free air from perforated, necrotic bowel.

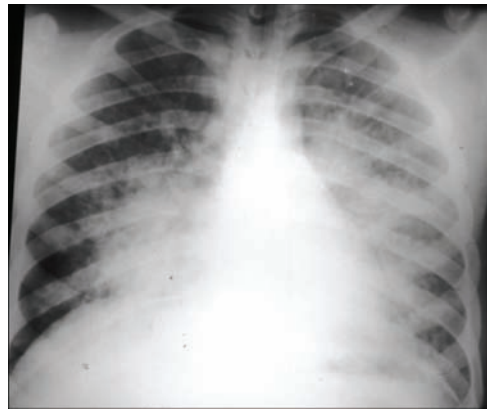


Figure 9.4 Noncardiogenic Pulmonary Edema: Crack Cocaine Injection. Frontal chest radiograph that demonstrates normal size and configuration of the cardio-mediastinal silhouette and bilateral diffuse pulmonary edema following the intravenous injection of crack cocaine. Noncardiogenic pulmonary edema may also follow opioid overdoses with the same radiographic patterns. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

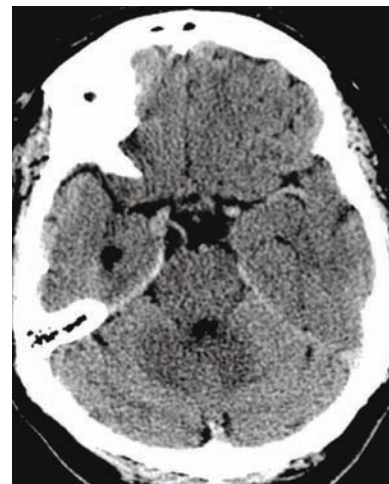


Figure 9.5 Intracranial Aneurysm: Crack Cocaine Inhalation. Cranial computerized axial tomogram (CT) at the level of the pons and the superior fourth ventricle in a crack cocaine abuser that demonstrates a right parasellar hyperdense rounded area consistent with a saccular aneurysm of the right posterior communicating artery. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

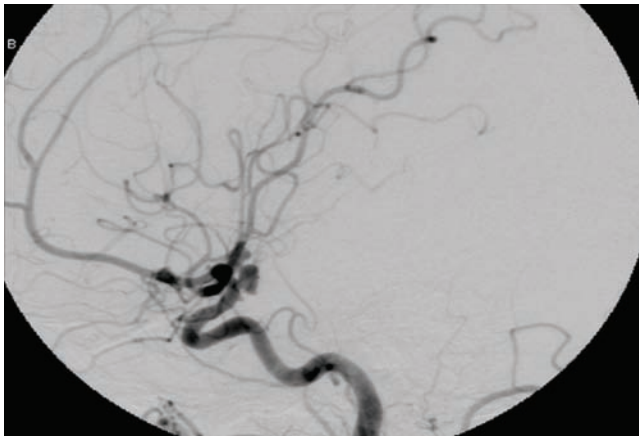


Figure 9.6 Intracranial Aneurysm: Crack Cocaine Abuser. Digital subtraction arteriogram in a lateral projection following radiographic contrast injection into the left internal carotid artery of a crack cocaine abuser that demonstrates a saccular aneurysm of the left posterior communicating artery. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

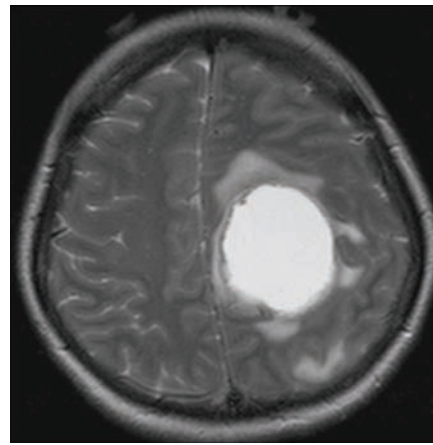


Figure 9.8 Septic Cerebral Emboli with Brain Abscess. Axial T1-weighted magnetic resonance image (MRI) of the brain at the level of the centrum semiovale that demonstrates a large cystic lesion with surrounding halos of vasogenic edema consistent with multiple septic emboli and resulting cerebral abscess in an intravenous crack cocaine abuser. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)



Figure 9.7 Intracranial and Interventricular Hemorrhage: Crack Cocaine Inhalation. Noncontrast computerized axial tomogram (CT) of the brain at the level of the third ventricle in a crack cocaine abuser that demonstrates a hyperdense lesion in the left basal ganglia, asymmetry of the left frontal ventricular horn, and interventricular hemorrhage in the right ventricular horn consistent with hypertensive intracranial hemorrhage with disruption into the ventricular system. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)



Figure 9.9a Pneumomediastinum Following Crack Cocaine Inhalation. Frontal (9.9a) and lateral (9.9b) chest radiographs that demonstrate radiolucencies throughout the left lung interstitium, mediastinum, and base of the neck consistent with pulmonary interstitial emphysema, pneumomediastinum, and subcutaneous soft tissue emphysema following crack cocaine inhalation. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

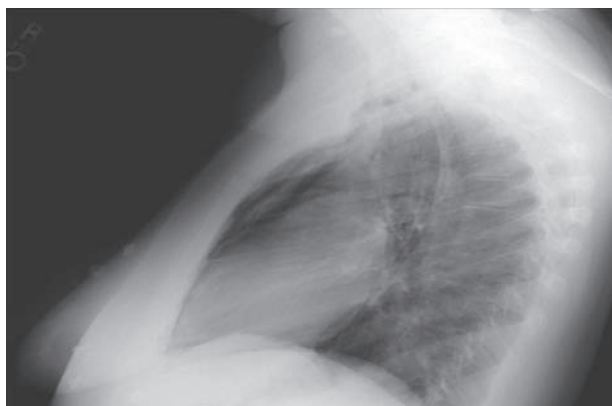


Figure 9.9b Pneumomediastinum Following Crack Cocaine Inhalation. Frontal (9.9a) and lateral (9.9b) chest radiographs that demonstrate radiolucencies throughout the left lung interstitium, mediastinum, and base of the neck consistent with pulmonary interstitial emphysema, pneumomediastinum, and subcutaneous soft tissue emphysema following crack cocaine inhalation. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)



Figure 9.10 Dissecting Thoracic Aneurysm. Contrast-enhanced, T1-weighted, sagittal-oblique, computerized axial tomogram (CT) of the chest that demonstrates an intimal flap dividing the descending thoracic aorta into true and false lumens consistent with dissection thoracic aneurysm Type B in an intravenous cocaine abuser. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

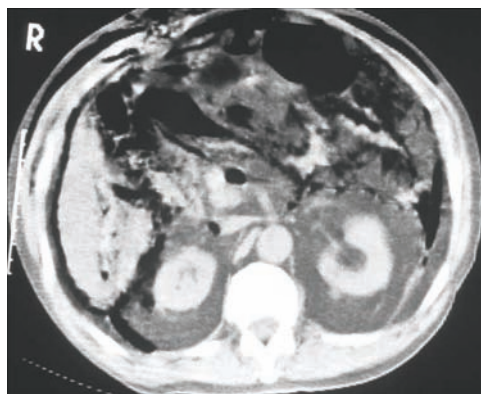


Figure 9.11 Fatal Mesenteric Infarction with Small Bowel Perforation. Noncontrast, computerized axial tomogram (CT) of the abdomen at the level of the uncinate process of the pancreas that demonstrates bowel gas in the main portal vein and its intrahepatic branches, extraperitoneal emphysema in the pro-peritoneal fat space and posterior pararenal space, pneumoperitoneum, and subcutaneous soft tissue emphysema following acute mesenteric infarction and subsequent small bowel perforation in an intravenous cocaine abuser. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

- MRI: Dissecting aortic aneurysm, pneumatosis intestinalis, portal and mesenteric venous air emboli.

Clinical Findings: CT, Radiographic, and MRI

- Crack cocaine inhalation: intracranial and interventricular hemorrhage.
- Intravenous crack cocaine abuse: septic cerebral emboli with multiple brain abscesses.
- Crack cocaine inhalation: radiolucencies throughout the left lung interstitium.
- Intravenous crack cocaine abuse: dissection thoracic aneurysm.
- Intravenous cocaine abuse: fatal mesenteric infarction with small bowel perforation.

General Overdose Management

General Principles

- Secure airway and control motor hyperactivity and seizures with benzodiazepines; barbiturates and neuromuscular paralysis with non-depolar-

izers (avoid succinylcholine — hyperkalemia, rhabdomyolysis unopposed).

- Coma cocktail: 1 g/kg D₅₀W and 100 mg thiamine IV.
- Externally cool: Ice-water baths.
- Avoid all neuroleptics, especially phenothiazines and succinylcholine, which could exacerbate rhabdomyolysis and increase K.
- Treat SVTs with calcium channel blockers (CCBs); treat QRS widening with NaHCO₃; and treat torsades de pointes with Mg.
- Avoid beta-blockers, which could precipitate unopposed alpha-agonist effects.

Enhanced elimination

- Initial AC and sorbitol, both at 1 g/kg, followed by MDAC for both body packers and body stuffers; monitor packers for packet rupture and need for surgical exploration.
- Consider whole-bowel irrigation (WBI) with polyethylene glycol electrolyte solution (PEG-ELS) for hemodynamically stable packers and stuffers.
- Hydrate while monitoring central venous pressure (CVP)–pulmonary artery pressure (PAP) and alkalize urine with NaHCO₃ drip to protect kidneys from rhabdomyolysis-induced myoglobinuria and high risk of acute tubular necrosis (ATN).

Specific Overdose Management

Cardiovascular Toxicity

- Hypertension: O₂, benzodiazepines for sedation, vasodilatation with rapidly acting peripheral vasodilators—phentolamine, nitroglycerine (NTG), and sodium nitroprusside (SCN).
- Pulmonary edema: O₂, furosemide, morphine sulfate (MS), NTG.
- Angina: O₂, benzodiazepines (BZs), MS, acetylsalicylic acid (ASA), NTG, CCBs, (verapamil > diltiazem), avoid beta-blockers.
- ST and SVT: O₂, BZs, CCBs, adenosine.
- VT and VF: O₂, BZs, NaHCO₃, cardioversion, defibrillation, consider lidocaine (avoid bretylium due to its initial adrenergic response).

CNS Toxicity

- Hyperthermia: O₂, ice water baths, BZs (lorazepam > diazepam), vasodilators, nondepolarizing muscle relaxants, dantolene.
- Agitation: Sedation with BZs and barbiturates, if indicated.
- Rhabdomyolysis: Hydrate while monitoring CVP-PAP, alkalize urine with NaHCO₃, institute osmotic diuresis with mannitol, consider hemodialysis if ATN imminent.

Management: Body Packers vs. Stuffers

Body Packers

- Confirm cocaine packs by abdominal x-ray.
- Institute ECG monitoring.
- Activated charcoal (AC) and cathartic, then multi-dose activated charcoal (MDAC) to reduce absorption and enhance elimination.
- Whole-bowel irrigation (WBI) with polyethylene glycol electrolyte solution (PEG-ELS) to reduce gastrointestinal mucosal contact time, speed transit, and increase elimination.
- Surgical removal for symptomatic patients with packet rupture or intestinal obstruction.
- Follow-up imaging with abdominal x-rays; consider barium enema.

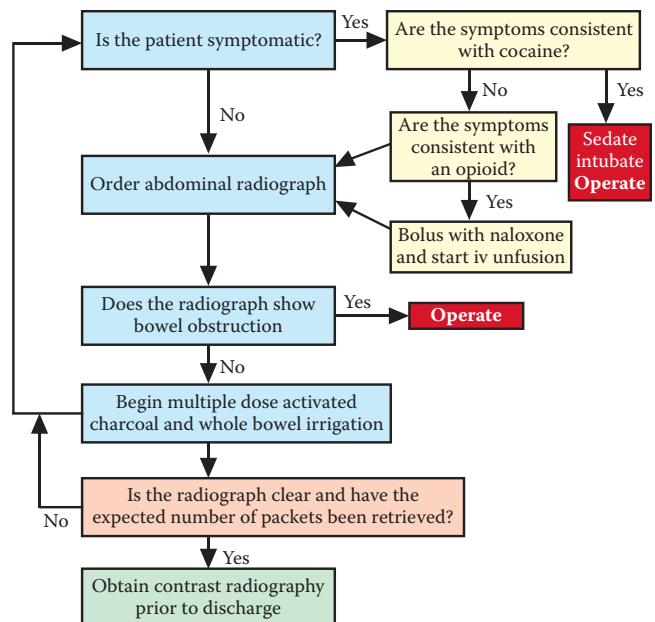


Figure 9.12 Management: Cocaine v. Heroin Body Packers. A flow chart outlining the clinical practice management strategies for body packers of cocaine or heroin.



Figure 9.13 Phentermine-Fenfluramine (Amphetamine) Cardiomyopathy. Digital subtraction frontal chest radiograph that demonstrates diffuse dilated cardiomegaly, predominantly of the left-sided cardiac chambers consistent with amphetamine-induced dilated cardiomyopathy in an obese patient taking an oral phentermine-fenfluramine combination for weight loss. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Body Stuffers

- Confirm by abdominal x-ray.
- Immediate orogastric lavage for recent ingestions.
- Institute ECG monitoring.
- AC and cathartic, MDAC to reduce absorption and increase elimination.
- WBI with PEG-ELS to reduce gastrointestinal mucosal contact time, speed transit, and increase elimination.
- Surgical removal for obstructed patients (ileocecal valve).
- Follow-up imaging with abdominal x-rays.

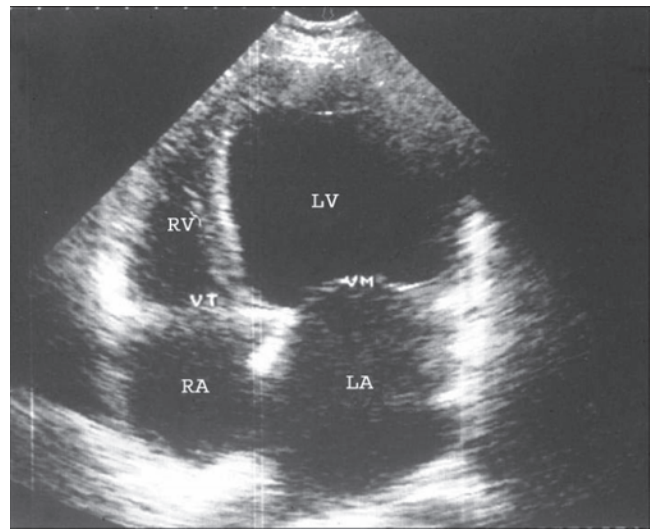


Figure 9.14 Phentermine-Fenfluramine (Amphetamine) Cardiomyopathy with Mitral Valve Prolapse. A cardiac ultrasound examination that demonstrates diffuse cardiomegaly predominantly of the left-sided cardiac chambers with mitral valve prolapse in an obese patient taking an oral phentermine-fenfluramine combination for weight loss. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Amphetamines

Pharmacology

- Mechanism: (1) Direct central release of catecholamines, particularly norepinephrine (NE) and dopamine, from presynaptic terminals; (2) competitive inhibition of catechol reuptake at adrenergic terminals; (3) central serotonin 5-hydroxytryptamine (HT) release at higher doses.
- NE effects: α - and β -adrenergic stimulation produce anorexia and alerting effects.
- 5-HT effects: Altered perception, psychosis, agitation, hallucinations, seizures.
- Metabolic: Lipid-soluble, high volume of distribution (V_d), increased active metabolites, no catechol-o-methyltransferase (COMT) biodegradation.

Abuse

- Prescription: Used for attention deficit hyperactive disorder (ADHD), narcolepsy, and weight loss.
- Illicit: Methamphetamine (ice, speed) — most common illicit drug produced by clandestine drug labs; primary ingredient = ephedrine, adulterants = Pb and Hg.
- Designer: Methylene-dioxymethamphetamine (MDMA) (Ecstasy, Adam) and methylene dioxyethamphetamine (MDEA, Eve).
- International: (1) khat: active agent = cathinone, Arabia and East Africa (Somalia) = euphoria, alertness, anxiety, hyperactivity; (2) ma-huang: Chinese ephedrine used as a bronchodilator for asthmatics and COPD patients and for sports performance enhancement. Banned by Olympics.

Prescription vs. Designer

- Prescription amphetamines:
 - Attention deficit-hyperactivity disorder (ADHD) and narcolepsy: Amphetamine,

dextroamphetamine, methamphetamine, methylphenidate (Ritalin® = most popular prescribed drug for preteens with ADHD), pemoline.

- Weight reduction: Amphetamine, dextroamphetamine, methamphetamine, dexfenfluramine, phentermine and fenfluramine (phen-fen combination: withdrawn by the FDA due to increased risks of pulmonary hypertension and valvular heart disease).
- Pure methamphetamine = ice or speed, methamphetamine.
- Designer amphetamines:
 - All designer amphetamines are potent central serotonin releasers; popular at all-night Rave Parties, often combined with ketamine.
 - Dimethoxyamphetamine: DOM or STP.
 - Methylene-dioxyamphetamine: MDA, love drug.
 - Methylene-dioxymethamphetamine: MDMA, Ecstasy, or Adam.
 - Methylene-dioxyethamphetamine: MDEA, Eve.

Acute vs. Chronic Amphetamine Toxicity

- Acute toxicity:
 - CNS > cardiovascular > pulmonary:
 - CNS: Mydriasis, anorexia, euphoria, psychosis, hyperthermia → diaphoresis, headache, agitation-hyperactivity → tremor, seizures → muscle rigidity → choreoathetosis → rhabdomyolysis → myoglobinuria → acute tubular necrosis → acute renal failure.
 - Cardiovascular: Hypertension, tachycardia, tachydysrhythmias, vasospasm, angina, myocarditis, and myocardial infarction (MI).
 - Pulmonary: Tachypnea, pulmonary vasoconstriction, and pulmonary hypertension.

- Chronic toxicity:
 - Cardiovascular and pulmonary: Catecholamine-induced dilated and valvular cardiomyopathies, mitral regurgitation (phen-fen), pulmonary hypertension (phen-fen), necrotizing vasculitis with ischemic colitis.
 - CNS: Permanent dopaminergic and serotonergic neurotransmitter depletion-induced encephalopathy.
 - Labs: Hyperglycemia, leukocytosis, elevated liver function tests (LFTs), elevated creatine phosphokinase (CPK) from rhabdomyolysis with myoglobinuria. False-positive urine drug screens may result from ephedrine, pseudoephedrine, or phenylpropanolamine (PPA), often found in over-the-counter (OTC) cold medications.
- Administer coma cocktail, without naloxone: 1 g/kg D₅₀W and thiamine 100 mg IV.
- Avoid all neuroleptics, which may exacerbate hyperthermia and lower seizure thresholds; cause dystonia and choreoathetosis with neuroleptic malignant syndrome; and may precipitate tachydysrhythmias due to quinidine (Type IA) effects. Avoid beta-blockers, which could precipitate unopposed alpha-agonist activity.
- Monitor for rhabdomyolysis with serum CPK levels and urinary myoglobin levels.

- Specific treatment:
 - Agitation and restlessness: BZs, such as IV diazepam.
 - Seizures: BZs > barbiturates > muscle relaxants (often, patients continue to manifest seizure activity on EEG and require prolonged anticonvulsant therapy).
 - Hyperthermia: Sedation and external cooling.
 - Oral ingestions: AC and sorbitol, both 1 g/kg.
 - Hypertension: Initially sedate with BZs, consider peripheral vasodilators for ease of titration — phentolamine, nitroglycerin, and sodium nitroprusside.

Overdose Management

- General management:
 - Restrain and sedate with BZs.
 - Rapid external cooling with ice-water baths; consider dantrolene IV.
 - AC for recent oral ingestions.

Phencyclidine (PCP)

History of PCP

- Developed in the 1950s as a dissociative anesthetic for painful diagnostic procedures; associated with post-operative psychomimesis, including hallucinations and sleep disturbances.
- Some of the early congeners of PCP are still in use today as dissociative anesthetics, primarily ketamine.
- PCP was introduced to the San Francisco drug scene in the 1960s as the PeaCePill, hence the abbreviation “PCP.”

Pharmacology of PCP

- Pharmacology: Highly lipid-soluble weak base; 65% plasma protein-bound; large volume of distribution of 6.2 L/kg; hepatically metabolized to inactive metabolites; renal excretion.
 - Mechanism: N-methyl-D-aspartate (NMDA) receptor antagonist, like ketamine and dextromethorphan, which inhibits the binding of glutamate to NMDA receptors centrally.
- Street use: Sold as tabs, caps, or rock salt-like crystals and abused by smoking, insufflation, and ingestion.

Clinical Manifestations

- Ophthalmic: Exception: PCP is the only NIDA-5 drug of abuse to cause miosis (all the rest cause mydriasis) — with blank stare, dysconjugate gaze, and nystagmus-horizontal, vertical, and rotatory; nystagmus is pathognomonic of PCP abuse.
- CNS: Disorientation, dysphoria, paranoia, dysarthria, jargonaphasia, auditory and visual hallucinations, agitation, hyperactivity, tremor, seizures, dystonia, torticollis, choreoathetosis, facial grimacing, opisthotonos, rhabdomyolysis, myoglobinuria, ATN, ARF.

- Cardiorespiratory: Hypertension, sinus tachycardia, no cardiorespiratory depression, tachypnea.
- Renal: ATN, ARF.

Lab Findings

- WBC: Leukocytosis.
- Lytes: Hyperkalemia.
- Glucose: Hypoglycemia.
- Arterial Blood Gases (ABGs): Metabolic acidosis.
- Enzymes: Elevated muscle enzymes from rhabdomyolysis, LDH, and CPK, often associated with myoglobinemia and myoglobinuria.
- Urine: False-positive urine PCP toxicity screens may result from co-ingestions with ketamine and dextromethorphan; both are also NMDA antagonists.

Management of PCP Overdose

General Management

- Restrain and sedate with BZs.
- Administer 100 ml D₅₀W and 100 mg thiamine IV.
- Avoid syrup of ipecac (epileptogenic) and sedation with neuroleptics (increased temperature, decreased seizure threshold, can induce dystonias and neuroleptic malignant syndrome).
- Orogastric lavage followed by AC (1 g/kg) and sorbitol (1 g/kg).
- MDAC preferred over continuous NG suction.

Specific Treatment

- Monitor for elevated CPK and myoglobinuria, as rhabdomyolysis is associated with high case fatality rates (CFRs).
- If myoglobinuria occurs, protect kidneys with hydration, osmotic diuretics (mannitol), and urinary alkalization with NaHCO₃.

Lysergic Acid Diethylamide (LSD)

Common Hallucinogens

- Lysergamides: All natural and synthetic ergot alkaloid derivatives (*Claviceps purpurea*), like LSD, and morning glory seeds.
- Indolealkylamines: Mushroom psilocybin and psilocin; bufotenine but more likely, methoxydimethyltryptamine from *Bufo alvarius* toads.
- Phenylethylamines: Mescaline from peyote cactus, all amphetamines (especially the serotonin [5-HT] releasers, MDMA and MDEA).
- Cannabinols: Delta-9-tetrahydrocannabinol (THC) in marijuana and hashish.

LSD Pharmacology

- Pharmacology: Colorless, tasteless, and odorless powders that are rapidly absorbed mucosally; 80% protein bound; hepatically metabolized with no active metabolites and short durations of action; terminated by renal excretion.
- Mechanism: All act as serotonin releasers and agonists, usually by promoting presynaptic serotonin release in the limbic system.

Clinical Manifestations

Acute Hallucinogen Toxicity

- Initial autonomic effects: Sympathomimetic with LSD (anxiety, tachycardia, hypertension, mydriasis, tremor, nausea, flushing, chills), but gastrointestinal (nausea and vomiting) with peyote; then a constellation of mydriasis, dizziness, diaphoresis, piloerection, ataxia, tachypnea, hypertension, and tachycardia.
- Later psychological effects: Emotional lability = euphoria–dysphoria, perceptual distortions, visual (“psychedelic” colors) > auditory (sounds magnified) > tactile > olfactory hallucinations.

Chronic Hallucinogen Toxicity

- Preexisting psychiatric illnesses predispose to chronic mental disturbances.
- Extended psychoses possible: Schizophrenia.
- Recurring panic reactions: Best managed by reassurance and support.
- Hallucinogen persisting perceptual disorder (HPPD): aka “purple haze” = recurrence of flashbacks of earlier “bad trips,” triggered by exercise, stress, or illness.

LSD Intoxication

General Management

- “Coma cocktail” IV: 100 mL D₅₀W and 100 mg thiamine and 2 mg naloxone; secure airway.
- AC and sorbitol (both 1 g/kg): For recent ingestions; ineffective once hallucinations begin.
- Acute panic reactions: Quiet room, no stimuli, reassurance by nonjudgmental advocate.
- “Bad trip” dysphoria: Sedation with BZs.
- Avoid excessive physical restraint: Secondary to rhabdomyolysis risks with high case fatality rates (CFRs).

Specific Treatment

- Hypertension: BZs initially, then vasodilators = phentolamine, nifedipine, sodium nitroprusside.
- Avoid all neuroleptics: May produce α -block with hypotension, hyperthermia, and reduced seizure threshold with convulsions, or precipitate neuroleptic malignant syndrome.
- Avoid β - and mixed α - and β -blockers: Because of risks of unopposed α -adrenergic-mediated hypertension.
- Hyperthermia: Aggressive external cooling, IV hydration, BZs and skeletal muscle relaxants (MRs); consider dantrolene.
- Monitor for rhabdomyolysis: Elevated CPK, myoglobinuria, protect renal function with hydration, osmotic diuresis, and urinary alkalization.

Marijuana

Epidemiology

- Marijuana is an oily, dried fibrous material obtained from the Indian hemp plant, *Cannabis sativa*.
- The most commonly used illegal substance in the United States.
- The most commonly abused substance in the world after nicotine, alcohol, and caffeine.
- Considered a “gateway drug” by the DEA, NIDA, and the Substance Abuse and Mental Health Services Administration (SAMHSA).

Pharmacology

- Delta-9-THC is the psychoactive component.
- Hashish (smoked in pipes) and hashish oil (mixed with tobacco and smoked): All are Cannabis derivatives that contain higher concentrations of THC.
- THC is transported to the brain within 15 seconds of smoking to occupy specific cannabinoid receptors in the cerebral cortex.

Acute vs. Chronic Marijuana Toxicity

Acute Marijuana Toxicity

- Physiological effects: Dose-related tachycardia, blood pressure remains stable, increased appetite, dry (cotton) mouth, conjunctival injection, reduced intra-ocular pressure, bronchodilation, weakness, muscle tremors, urinary retention, low testosterone levels — impotence.
- Psychological effects: Dose-related euphoria, relaxation, sensory alterations. Preexisting psychopathology may predispose to transient, acute psychotic reactions with paranoid delusions and hallucinations.

Chronic Marijuana Toxicity

- Tolerance and dependence: Resulting from repeated use.
- Withdrawal syndrome: Irritability, restlessness, insomnia, and appetite loss.
- COPD, oral and lung cancer: Smoking-induced.
- Congenital toxicity: Neonatal and early childhood neurobehavioral and developmental disturbances.
- Male infertility: The result of combinations of low testosterone levels, low sperm counts, reduced sperm motility, and greater abnormal sperm morphology.

Management of Marijuana Intoxication

- Motor vehicle and other transportation-related accidents: Marijuana is detected in 11–33% of cases (including mass transit and train accidents) and associated with a prolonged (≥ 24 hours) loss of judgment and motor skills needed for safe vehicular operation.
- Acute psychotic reactions: Sedation with BZs.
- Pneumomediastinum: Rare and the result of deep inhalation with alveolar overdistension and rupture; supportive management with O₂.

"Date-Rape" Drugs

"Date-Rape": GHB

Toxicokinetics

- Street names: Liquid Ecstasy, Easy Lay.
- GHB is an active GABA metabolite: GHB is a naturally occurring CNS (brain) metabolite of GABA, the central inhibitory neurotransmitter.
- Rapid oral absorption: Peak onset in 15 minutes; duration 1.5–2 hours.
- Gamma-butyrolactone (GBL): An active hepatic (tricarboxylic acid cycle) metabolite of GHB.

Clinical Manifestations

- CNS: Initial relaxation, tranquility, disinhibition; followed rapidly by loss of consciousness, drowsiness, dizziness, disorientation, delirium, amnesia, rarely seizures.
- Cardiopulmonary: Bradycardia, mild hypotension, transient respiratory depression.
- Gastrointestinal: Vomiting.

Methods of Use and Abuse

- Licit use: Narcolepsy, not FDA-approved in the United States.
- Ineffective use: Thought to potentiate the anabolic effects of growth hormone and often abused by body builders to promote rest, fasting, fat metabolism, muscle mass, and high growth hormone levels.
- Illicit use: "Date-rape."

General Management of Overdose

- Airway protection: Monitor oxygenation and ventilation.
- Consider coma cocktail: Flumazenil and naloxone ineffective.
- Atropine: For bradycardia.
- Consider physostigmine: For reversal of CNS depression.

Flunitrazepam

Toxicokinetics

- Rohypnol®: Foreign trade name, not FDA-approved; U.S. street drug; a tasteless, odorless powder that dissolves rapidly in alcohol.
- Short-acting benzodiazepine: ≥ 10 times more potent than diazepam.
- Rapid oral absorption: Peak onset in 15–20 minutes; duration 4–6 hours.

Clinical Manifestations and Management

- Profound CNS depression with maintenance of stable vital signs; characteristic of BZs.
- Antero-grade amnesia common.
- General overdose management: Supportive, protect airway, monitor oxygenation and ventilation.
- Antidote: Flumazenil.

Miscellaneous Date-Rape Drugs

- Ketamine: A sympathomimetic amine similar to phencyclidine (PCP) that rapidly induces dissociative anesthesia with sedation, delirium, hallucinations, and respiratory depression. Seizures, tachyarrhythmias, and cardiac arrest are possible. Therapy requires supportive care, ECG monitoring, and quiet recovery, often with BZ sedation.
- Chloral hydrate: A halogenated hydrocarbon alcohol hepatically metabolized by alcohol dehydrogenase to trichloroethanol that has a prolonged half-life of 4–14 hours and potentiates alcohol intoxication. Also known as knock-out drops or a "Mickey Finn."

Poisonings with Cardiovascular Medications

Chapter Outline

Cardiac glycosides

- Etiology
- Mechanisms
- Pharmacology
- Pathophysiology
- Toxic effects: adults vs. children
- Lab diagnosis
- General management
- Specific management
- Digoxin-specific Fabs

Beta-blockers

- Overdose epidemiology
- β -Adrenergic physiology
- Classification (mean half-life = 5 hours)
- Toxicity
- Differential diagnosis: Drug-induced bradycardia
- General overdose management
- Specific management of severe toxicity

Calcium channel blockers

- Epidemiology of CCB overdose
- CCB physiology
- CCB pharmacology
- CCB classification
- CCB indications
- Clinical manifestations
- General overdose management
- Specific management

Miscellaneous antihypertensives

- Sympatholytics
- Diuretics
- Vasodilators
- Angiotensin classification blockers

Cardiac Glycosides

Etiology

- Digoxin is most often implicated.
- Rarely implicated cardiac glycosides: Digitoxin, ouabain, lanatoside C (now used infrequently).
- Plant glycoside ingestions: Foxglove, oleander, lily-of-the-valley, red squill.
- Toad skin venom: Presumed aphrodisiacs secreted by Bufo toads (Family Bufonidae) that contain bufotoxins, especially from the bufadienolide class. Common U.S. species include Colorado River toad (*Bufo Alvariusi*), cane toad (*Bufo marinus*), and the American toad.

Mechanisms

- Inhibition of the Na-K ATPase-dependent myocardial sarcolemmal pump.
- Positive inotropic effect from elevated intracellular (cytosolic) Ca during systole.
- Direct and indirect vagomimetic effects = cause the most common side effects: nausea, vomiting, bradycardia, heart block.
- Peripheral vasodilation and reduced afterload.

Plant Glycosides

- Foxglove (*Digitalis purpurea*)
- Oleander (*Nerium oleander*)

Natural Glycosides

- Lily-of-the-Valley (*Convallaria majalis*)
- Cane toad (*Bufo marinus*)

Pharmacology

- Slow absorption and onset: IV 5–30 minutes; orally 1.5–6 hours.
- 25% protein binding.
- High volume of distribution (V_d): 6–7 L/kg adults, even greater in children.

- Half-life: 1.6 days.
- Limited hepatic metabolism and enterohepatic circulation.
- 60–80% renal excretion.
- Narrow therapeutic index: 0.5–2.0 ng/mL.

Pathophysiology

- At toxic doses, digoxin suppresses the sinoatrial (SA) node, increasing atrial and ventricular automaticity causing extrasystoles and tachydysrhythmias: junctional tachycardia, atrial fibrillation, atrial flutter, and ventricular tachycardia — ventricular fibrillation, pathognomonic bidirectional ventricular tachycardia (torsades de pointes).
- Reduces conduction velocity in atria, ventricles, and atrioventricular node = increased PR interval, sinus bradycardia, sinoatrial (SA) and junctional blocks, and atrioventricular blocks.
- Noncardiac: Anorexia, nausea, vomiting, cramps, confusion, hyperkalemia (blocks cytosolic K entry), hypomagnesemia.

Toxicity effects: Adults vs. Children

Adults

- Cardiac: Sinus bradycardia, atrioventricular (AV) block, nonparoxysmal atrial tachycardia, premature ventricular contractions (PVCs), bigeminy, bidirectional ventricular tachycardia (torsades de pointes), ventricular fibrillation.
- Noncardiac: Anorexia, crampy abdominal pain, nausea and vomiting, confusion, dizziness, fatigue, lethargy, delirium. Unique visual disturbances: halos, yellow and green flashes and objects, darkened and blurred vision.

Children

- Cardiac: Bradycardia, 1st–2nd degree AV blocks, junctional rhythm, SA arrest, SA blocks,

AV junctional tachycardia, rarely ventricular fibrillation.

- Noncardiac: Lethargy and vomiting.

Lab Diagnosis

Serum Digoxin Levels

- Very narrow therapeutic index: 0.5–2.0 ng/mL.
- Heightened toxicity caused by electrolyte changes and certain drugs: Decreased levels of K–Mg–Ca, elevated Na, alkalosis, hypothyroidism, decreased level of O₂, catecholamines, calcium channel blockers (CCBs), quinidine, amiodarone, diuretics (via hypokalemia), enzyme inhibition by cimetidine.
- Increased by digoxin-like immunoreactive substances (DLIS) and digoxin-Fabs.
- Polyclonal digoxin radioimmunoassays (RIAs): To clarify true increase [digoxin].

Endogenous Digoxin-Like Immunoreactive Substances (DLIS) Are Associated with:

- Renal insufficiency.
- Pregnancy.
- Liver disease.
- Heart disease: Congestive heart failure (CHF).
- CNS insults: Subarachnoid hemorrhage (SAH).
- Endocrinopathies: Insulin dependent diabetes mellitus (IDDM) and acromegaly.
- Neonates: Stress and elevated serum bilirubin levels.
- Adults: Stress and drugs = spironolactone (via hyperkalemia).

General Management

- Discontinue digoxin, gastrointestinal decontamination, especially with AC.
- Orogastric lavage preferred to emesis in a digoxin-toxic patient already vomiting.
- AC and sorbitol, then MDAC up to 1 g/kg every 2–4 hours. Slow absorption and an enterohepatic circulation make digoxin very amenable to decontamination, with both AC and MDAC.
- Steroid-binding resins: Cholestyramine and colestipol to bind digoxin and interrupt enterohepatic circulation along with MDAC.

- Hemoperfusion and hemodialysis ineffective due to high molecular weight and increased volume of distribution.

Specific Management

- Digoxin-specific antibody fragments — Fabs (DigiBind®): Will decrease free digoxin but elevate total serum digoxin levels; Fabs will also decrease levels of K and increase excretion of Fab-bound digoxin.
- K > 5 mEq/L: Fab > insulin and glucose > NaHCO₃ > sodium polystyrene sulfonate.
- Supraventricular tachycardia (SVT): Fab preferred over β-blockers.
- Atrioventricular (AV) block: Fab preferred over pacemaker.
- Ventricular tachycardia (VT)/ventricular fibrillation (VF): Cardioversion/defibrillation preferred over Fab, phenytoin, and lidocaine.
- Contraindicated medications: Isoproterenol and, especially, calcium, due to increased intracellular calcium stores.

Digoxin-Specific Fabs

Indications

- Rising K or K > 5 mEq/L at any time.
- Severe ventricular dysrhythmias: VT, VF, torsades de pointes.
- Progressive bradydysrhythmias refractory to atropine.
- Serum [dig] > 10–15 ng/mL anytime.
- Ingestion of > 4 mg of digoxin by a child; and > 10 mg by adult.

Dose Calculations for Digoxin Fab Therapy

- Each vial of DigiBind® contains 38 mg purified digoxin-specific Fabs that will bind exactly 0.5 mg digoxin.
- Assume 80% bioavailability on absorption of ingested digoxin.
- Example: Adult 70 kg ingests 50 0.25-mg tabs; $0.25 \times 50 = 12.5$ mg digoxin ingested; $12.5 \times 0.80 = 10$ mg digoxin absorbed; $10/0.5 = 20$ vials DigiBind® are indicated.
- Give at least 5–20 vials of DigiBind® whenever treatment of digoxin toxicity is indicated.

Beta-Blockers

Overdose Epidemiology

- During 1989–1995, 5000 β -blocker overdoses were reported to the American Association of Poison Control Centers (AAPCC), with 15 adult deaths and no pediatric deaths.
- Children <6 years old accounted for 1/3 of all exposures, but no deaths.
- Intentional β -blocker overdose occurred most commonly with propranolol, frequently prescribed to patients with suicidal ideations = anxious, nervous, hyperactive, stressed out, often with migraine headaches and chronic pain syndromes or tremors.

β -Adrenergic Physiology

- Catecholamines (norepinephrine, epinephrine) stimulate their β -adrenergic receptors that are coupled to G proteins on myocardial, pulmonary, and vascular membrane surfaces.
- This stimulation increases intracellular cAMP, which in turn activates protein kinases, the ultimate end mediators of the cellular effects of β -receptor stimulation.

- There are three (3) types of β -receptors: β_1 , β_2 , and β_3 , with β_1 subserving the cardiovascular effects of increasing cardiac contractility, intra-cardiac conduction velocity, cardiac automaticity, and renal renin secretion.
- Specific β_1 -receptor stimulation causes the cardiovascular effects of increased cardiac contractility, intracardiac conduction velocity, cardiac automaticity, and renal renin secretion.
- Specific β_2 -receptor stimulation causes peripheral arteriolar vasodilation, pulmonary bronchodilation, hepatic gluconeogenesis, and glycogenolysis, increased insulin secretion with hypoglycemia, and increased uptake by muscle resulting in serum hypokalemia.
- β_3 -receptor stimulation probably mediates thermogenesis and lipolysis.
- Even the most selective β -blockers will lose their selectivity in overdose.

Classification (mean half-life = 5 hours)

Nonselective β -Blockers (β_1 and β_2)

- Labetolol (increased also an α_1 -blocker)
- Nadolol (half-life = 10 hours)

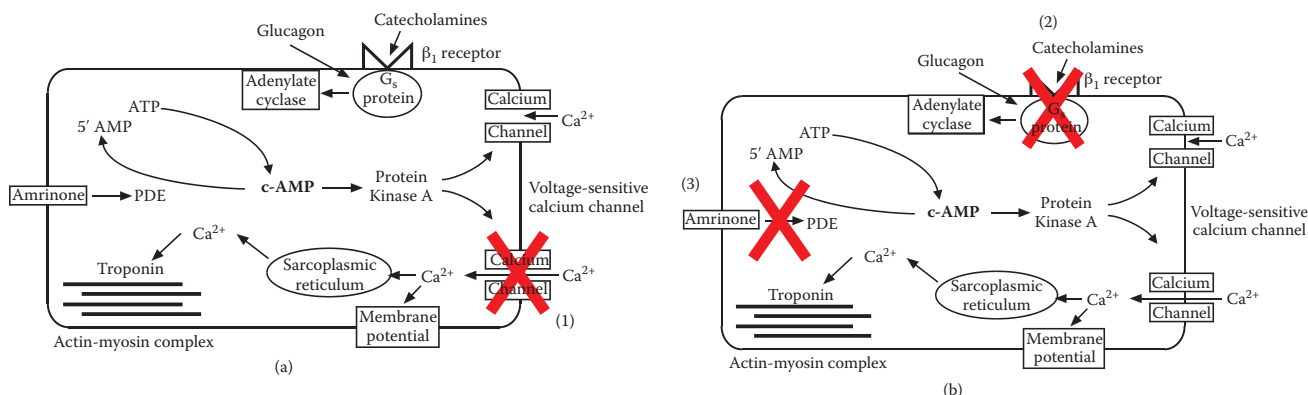


Figure 10.1 Cardiovascular adrenergic physiology and pharmacology. The cardiovascular molecular receptors and ionic channels and the mechanisms and sites of action of (1) calcium channel blockers, (2) beta-receptor blockers, and (3) phosphodiesterase inhibitors.

- Oxprenolol (exhibits intrinsic sympathetic activity [ISA])
- Pindolol (exhibits ISA)
- Propranolol (increased lipid solubility)
- Sotalol (increased half-life = 10 hours)
- Timolol

β_1 -Selective Blockers

- Acebutalol (ISA)
- Atenolol (increased H_2O solubility)
- Esmolol (very short-acting)
- Metoprolol

Indications

- Hypertension: β_1 -selective > nonselectives, which also block bronchodilation and peripheral vasodilation and could exacerbate bronchospasm in obstructive pulmonary disease and lower extremity claudication in peripheral vascular disease.
- Angina: Reduce anginal attacks and decrease post-myocardial infarction mortality.
- Tachydysrhythmias: Used in theophylline overdose, but adenosine preferred over β -blockers.
- Tremor: Propranolol over prescribed agitation, stage fright, and panic attacks (“shakes”).
- Migraine headaches.
- Hyperthyroidism: β -blockers moderate the sympathetic, hyperdynamic effects of thyroid storm.

Side Effects

- Bronchospasm: Nonselectives prevent bronchodilation and promote bronchospasm in chronic obstructive pulmonary disease (COPD) patients.
- High anaphylaxis risk: Nonselectives block catechol’s ability to reduce mast cell degranulation in patients with atopic allergies.
- Hypoglycemia: All β -blockers mask sympathetic response to hypoglycemia and interfere with gluconeogenesis/glycogenolysis.
- Withdrawal: Rebound increased heart rate and elevated blood pressure on abrupt withdrawal can precipitate MI and CVA.

Toxicity

- Asymptomatic: 1/3 of all β -blocker overdoses.
- Mild toxicity: Bradycardia, mild hypotension, ECG — increased PR interval and widened QRS.
- Moderate toxicity: Sinus arrest, atrioventricular (AV) block, severe hypotension, hypoglycemia.
- Severe toxicity: All of the above and cardiovascular collapse, delirium, coma, seizures (especially with propranolol overdose), respiratory depression, bronchospasm in COPD patients, and possibly, asthmatics.

Differential Diagnosis: Drug-Induced Bradycardia

- β -Blockers: Hypotension, depressed mental status, slightly elevated K, ECG — prolonged PR interval and widened QRS.
- CCBs: Hypotension, preserved mental status, ECG — PR prolonged interval and widened QRS complex.
- Digoxin: Nausea and vomiting, hyperkalemia, hypertension, and mental status preserved; ECG — prolonged PR, ST changes, atrial then ventricular dysrhythmias.
- Na-channel blockers: Seizures, hypotension, depressed mental status, ECG — widened QRS complex.
- Cholinergics: SLUDGE, DUMBBELS, ECG — sinus tachycardia or paradoxical bradycardia.
- α -agonists: α_1 = phenylpropanolamine (PPA): Severe hypertension, intracranial hemorrhage (ICH), sinus bradycardia; α_2 = clonidine, imidazolines: cause an opioid toxidrome, with pinpoint miosis and sinus bradycardia.

General Overdose Management

- Asymptomatic: No ipecac, AC preferred over lavage with vagomimetic effects, WBI for sustained-release preps.
- Mild toxicity: All of the above and atropine for bradycardia and fluid bolus for hypotension.

- Moderate toxicity: All of the above and glucagon (hormone secreted by pancreatic α cells in response to decreased levels of glucose and elevated catechols); administer 2–5 mg bolus of glucagon IV push to bypass β -receptors and to increase intracellular cAMP; CaCl_2 IV up to 1 g; consider more atropine, up to 3 mg IV.

Specific Management of Severe Toxicity

- General management and invasive monitoring.
- Catecholamine infusion: Dobutamine (β_1) preferred over norepinephrine (NE) (α and β) and isoproterenol.
- Isoproterenol is the least preferred catecholamine due to peripheral vasodilation with hypotension (from β_2 stimulation).
- Add a phosphodiesterase inhibitor: Amrinone or milrinone to bypass β -receptors and increase intracellular cAMP restoring cardiac contractility.
- Consider IV insulin and glucose therapy.
- Consider ventricular pacing.
- Hemodialysis rarely indicated.

Calcium Channel Blockers

Epidemiology of CCB Overdose

- In 1995, there were over 8300 CCB overdoses, >1000 caused moderate to major toxicity, with 69 deaths, mostly from sustained-release preparations.
- CCBs are No. 3 in prescribed drug overdoses, after No. 1 TCAs/SSRIs and No. 2 opioids.
- In 1989, verapamil, diltiazem, and nifedipine were among the top-20 prescribed drugs.

CCB Physiology

- Cardiac and smooth muscle cells (GI and vascular) require active influx of Ca through L-type, voltage-sensitive Ca channels for excitation-contraction coupling (ECC) and cardiac, vascular, and intestinal muscle conduction and contraction.
- Skeletal muscle depends on its own intracellular Ca stores for ECC and is unaffected by CCBs.
- Ca influx also modulates myocardial conduction by stimulating spontaneous depolarization (phase 4) in SA node and propagating conduction from the SA node and through the AV node.

CCB Pharmacology

- CCBs block L-type, slow Ca channels in cardiac and smooth muscle cells.
- CCBs limit Ca entry into cardiac and smooth muscle cells, reducing excitation-contraction coupling and slowing intracardiac electrical conduction.
- Myocardial force of contraction and inotropy are decreased; conduction through the SA and AV nodes is reduced; vascular smooth muscle relaxes, causing peripheral vasodilation and lowered blood pressure.

- CCBs are well absorbed orally, hepatically metabolized and highly protein bound, and have increased volumes of distribution (not dialyzable).

CCB Classification

- Phenylalkylamines: Exert the greatest effects on SA and AV normal conduction and cause profound negative inotropic effects in overdose:
 - Verapamil (Calan®)
- Benzothiazepines:
 - Diltiazem (Cardizem®)
- Dihydropyridines: The largest, safest, and most frequently prescribed class of CCBs:
 - Nifedipine (Procardia®)
 - Nimodopine (Nimotop®)
 - Nicardipine (Cardene®)

CCB Indications

- Severe hypertension
- Tachycardias: atrial fibrillation, atrial flutter, reentrant supraventricular tachycardia (SVT)
- High peripheral vascular resistance (PVR) with hypertension and/or vasospastic conditions: Raynaud's phenomenon, Prinzmetal's angina, cardioesophageal spasm, vascular headaches, post-subarachnoid hemorrhage (SAH), cerebral vasospasm

Clinical Manifestations

Onset and Severity of Poisoning

- Toxicity presents within 2–3 hours post ingestion with regular-release preparations.
- Toxicity may be delayed 6–8 to 15 hours with sustained-release preparations with half-lives >48 hours.

- Co-morbidities: Congestive heart failure (CHF) and advancing age magnify predisposition to and severity of toxicity from CCB overdoses.

Forme Fruste Clinical Presentation

- Cardiovascular: Myocardial depression with bradycardia and peripheral vasodilation = hypotension, decreased myocardial conduction = AV block may progress to complete heart block.
- CNS: Lightheadedness, dizziness, fatigue, lethargy, syncope, and rarely, coma. Severe CNS depression uncommon. As opposed to β -blocker toxicity with heart block and profound CNS depression.
- Reduced insulin release = hyperglycemia.
- Pulmonary: Noncardiogenic pulmonary edema (NCPE) from increased transcapillary hydrostatic pressure.

General Overdose Management

- Gastrointestinal decontamination: No ipecac due to rapid deterioration in level of consciousness; immediate orogastric lavage within 1–2 hours.
- AC: 1 g/kg and cathartic, then MDAC, 0.5 g/kg, especially for sustained-release preparations.
- WBI: WBI with PEG-ELS for sustained-release preparations, 1–2 L via NG and antiemetic.
- Monitoring: ECG, good IV access.

Specific Management

- Atropine: 0.5 mg IV every 2–3 minutes, to 3 mg.
- 10% CaCl_2 : 3 times more ionic calcium activity than calcium gluconate, dose = calcium chloride: 1 gram IV (20 mg/kg); calcium gluconate: 3 grams IV (60 mg/kg).
- Vasopressor support: Epinephrine > norepinephrine > phenylephrine > dopamine > dobutamine (β_2) > isoproterenol (β_2).
- Glucagon: Bypasses β -receptor to increase cAMP; administer 2–5 mg IV push over 1 minute, infuse at 4 mg/hour.
- Phosphodiesterase inhibitor: Amrinone > milrinone to bypass β -receptor and to increase intracellular cAMP.
- Intra-aortic balloon pump > cardiopulmonary bypass > extracorporeal membrane oxygenation > pacemaker.
- Consider insulin and glucose therapy.

Miscellaneous Antihypertensives

Sympatholytics

Classification

- Central α_2 -agonists: Clonidine (Catapres®), α -methyldopa (Aldomet® a prodrug that induces central α_2 -agonist activity), imidazolines (eye/nose drops).
- Ganglionic blockers: Trimethaphan (Arfonad®)
- Peripheral adrenergic blockers: Guanethidine (Ismelin®), reserpine
- Peripheral α_1 -blockers: Prazosin (Minipress®)

Mechanisms, Indications, and Side Effects

- Reduce central sympathetic outflow: Indicated for hypertension, migraine, opioid/EtOH withdrawal, as nasal decongestants; side effects include withdrawal, rebound hypertension, α -methyldopa causes a Coombs and hemolytic anemia.
- Reduce postganglionic autonomic transmission: Often used for deliberate hypotension to limit surgical blood loss.
- Reduce NE release from distal nerve terminals: Initially used to treat hypertension, prior to newer antihypertensives.
- Block postsynaptic α_1 -receptors in vascular smooth muscle.

Toxicity

- α_2 -agonists: Opioid toxidrome = miosis, bradycardia; hypotension and CNS depression may follow initial paradoxical hypertension, and hypothermia; CNS depression = lethargy, somnolence, stupor.
- Ganglionic blockers: Hypotension, constipation, urinary retention.
- Peripheral blockers: Hypotension, orthostasis, drowsiness, diarrhea.
- Peripheral α_1 -blockers: Hypotension, syncope, orthostasis, CNS depression.

Management

- No ipecac, AC, whole-bowel irrigation (WBI) for clonidine patch ingestions, naloxone drip, IV fluids, sodium nitroprusside (SCN) for initial hypertension.
- Crystalloid fluid boluses, direct-acting vasopressors — NE > phenylephrine.
- Crystalloid fluid boluses and vasopressors (dopamine).

Diuretics

Classification

- Thiazides: HCTZ (Hydrodiuril®), chlorthalidone (Hygroton®).
- Loop diuretics: Furosemide (Lasix®), bumetanide (Bumex®), ethacrynic acid (Edecrin®).
- K-sparing diuretics: Triamterene (Maxzide®), spironolactone (Aldactone®).

Mechanisms, Indications, and Side Effects

- Limit Na and Cl reabsorption in distal convoluted tubule: Indicated for hypertension, diuresis.
- Limit K-Na-Mg reabsorption: Indicated for digoxin toxicity.
- Limit Na-K-Cl reabsorption in ascending loop: Indicated for diuresis.
- Limit Na and Cl reabsorption in distal convoluted tubule and collecting ducts, aldosterone antagonists: Indicated for diuresis.
- Side effects: Hyperuricemia (gout), hyponatremia, hypokalemia, ototoxicity; aldosterone antagonist may cause hyperkalemia and precipitate digitalis toxicity.

Toxicity

- Hypovolemia: From brisk diuresis.
- Electrolyte disturbances: Low serum Na, K, Cl, and Mg levels may be associated with altered mental status, muscle weakness, and digoxin toxicity.

Management

- Fluid replacement.
- Electrolyte replacement: Restore normal Na, Cl, K, and Mg levels; consider sodium polystyrene sulfonate binding agent for hyperkalemia from K-sparing diuretics; monitor digoxin levels.

Vasodilators

- Direct smooth muscle vasodilators:
 - Hydralazine (Apresoline®)
 - Minoxidil (Rogaine®)
 - Diazoxide (Hyperstat®)
 - Sodium nitroprusside (Nipride®)

Mechanisms, Indications, and Side Effects

- All: Produce vascular smooth muscle relaxation with peripheral vasodilation and triggering of baroreceptor-mediated tachycardia; main uses — hypertension.
- Management of toxicity: Fluids, α -pressors.
- Hydralazine: Same indications, and lupus syndrome possible as a side effect, as with procaineamide.
- Minoxidil: Same indications, and hair growth.
- Diazoxide: Same, and immediate increase in glucose in management of insulin and oral hypoglycemic overdoses.
- Sodium nitroprusside: Vasodilation via nitric oxide mechanism; cyanide (CN) toxicity possible (Lilly CN kit — sodium nitrite first, then sodium thiosulfate).

Angiotensin Blockers Classification

- Angiotensin converting enzyme (ACE) inhibitors: Captopril (Capoten®), enalapril (Vasotec®), lisinopril (Prinivil®), quinapril (Accupril®).
- Angiotensin II receptor blockers: Losartan (Cozaar®), valsartan.

Mechanisms, Indications, and Side Effects

- Angiotensin converting enzyme inhibitors: Block conversion of angiotensin I to II in lungs and vascular endothelium, reduced peripheral vascular resistance (PVR), lower blood pressure; indications — hypertension; side effects: reduced bradykinin breakdown in lungs, causing angioedema and cough.
- Management of toxicity: Epinephrine, H_1 -blockers, steroids.
- Angiotensin receptor blockers: Decrease formation of angiotensin II at vascular receptor sites; indications — hypertension; side effects: few, bradykinin metabolism unaffected, no angioedema and cough so common with ACE inhibitor therapy.

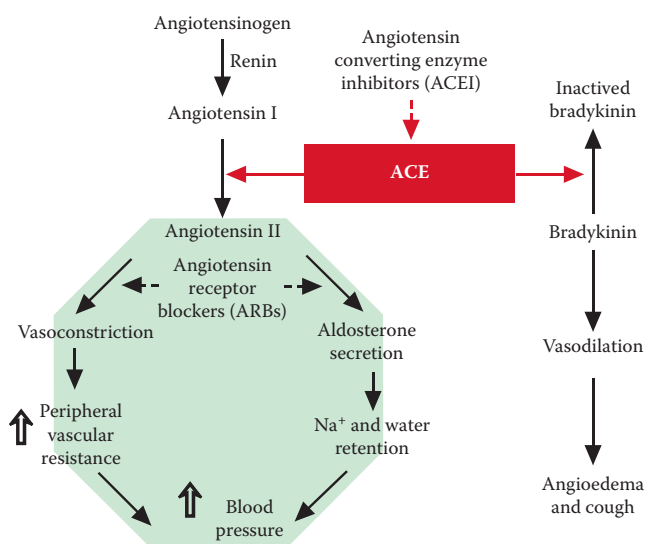


Figure 10.2 The renin-angiotensin-aldosterone pathway and mechanisms of action. Flow chart demonstrating the rennin-angiotensin-aldosterone (RAA) system and mechanisms of action and the sites of action of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs).

TABLE 10.1 Vaughan-Williams Classification of Antiarrhythmics

Class	Mechanisms	Toxicity	Examples
Class IA	Short-acting, open-state, Na channel block > K channel block	Widened QRS; prolonged QT, SA, and AV blocks; torsades	Quinidine Procainamide Disopyramide
Class IB	Increased effective refractory period; short-acting Na channel block	Biphasic CNS — cardiovascular toxicity — CNS > CV; little change in QRS and QT; sinus arrest; AV block	Lidocaine Mexilitene Tocanide Phenytoin Propafenone
Class IC	Prolonged Na, K, and Ca channel blocks	Widened QRS, prolonged QT, SA, and AV blocks, VT-VF	Ecinide Flecainide
Class II	β_1 and β_2 -blockers, selective (β_1) and nonselective (β_1 and β_2)	Prolonged PR, widened QRS, bradycardia, AV block, bronchospasm, hyperglycemia, and hypotension	Esmolol (β_1) Labetolol (β_1, β_2) Propranolol (β_1, β_2)
Class III	K channel blockers, prolonged depolarization and repolarization	Sinus bradycardia, profound negative inotropism, severe hypotension	Amiodarone (hypothyroidism, pulmonary fibrosis, corneal micro-deposits) Bretylium (initial hypertension)
Class IV	L-type Ca channel blockers	Bradycardia and hypotension, AV blocks, lethargy and vertigo, little CNS depression	Verapamil Diltiazem Nifedipine
Unclassified: Adenosine	Purine (adenosine) receptor agonist, very short half-life	Sinus arrest, asystole, bronchospasm, hypotension, methylxanthine-induced SVTs require larger doses due to adenosine receptor antagonism	Adenosine

Unclassified: Adenosine

- A naturally occurring nucleoside and G-protein with its own specific adenosine receptors; IV boluses of adenosine are indicated to rapidly terminate reentrant and theophylline-induced SVTs.
- Mechanisms: Provides an evanescent (10 sec) calcium entry block and increases AV nodal refractory period; reduces action potentials and reduces automaticity.
- Toxicities: Transient asystole, atrial fibrillation, hypotension, bronchospasm. All toxicities are potentiated by the antiplatelet agent, dipyridamole, an adenosine uptake inhibitor. Higher doses are required for methylxanthine overdoses due to adenosine receptor blockade.
- Treatment of toxicity: Supportive.

Class IA: Quinidine

- Mechanism: Na, K, and Ca channel blocker.
- Pharmacology: An amide local anesthetic, with excellent mucosal absorption, d-isomer of quinine, the antimalarial from cinchona bark; rapidly absorbed orally; high volume of distribution and protein binding.
- Toxicity: Prolonged QT interval and widened QRS complex, ventricular tachycardia, ventricular fibrillation, torsades, hypotension, seizures, noncardiogenic pulmonary edema, cinchonism.
- Treatment: Decontamination — no ipecac, orogastric lavage; IV fluids and vasoMech (a cardiac and peripheral Na channel blocker).

Miscellaneous Poisonings with Commonly Prescribed Drugs: Antibiotics, Cancer Chemotherapeutics, and Hypoglycemics

Chapter Outline

Antibiotics

Cancer chemotherapeutics

Hypoglycemics

Antibiotics: Outline

Antibiotics

- Penicillins
- Cephalosporins
- Aminoglycosides
- Chloramphenicol
- Vancomycin
- Fluoroquinolones
- Macrolides
- Sulfonamides
- Tetracyclines
- Antifungals

Antituberculosis agent toxicity

- TB and isoniazid (INH) epidemiology
- INH pharmacokinetics
- INH mechanisms and toxicity
- INH overdose management
- Chronic INH toxicity
- Other antituberculosis agents

Antimalarial agent toxicity

- Current antimalarials
- Quinine and cinchonism
- Quinine and quinidine overdose
- Chloroquine toxicity
- Other antimalarials

Antibiotics

Penicillins

Mechanism and Toxicity

- Mechanism: Penicillins are β -lactams that erode bacterial cell walls by inhibiting mucopeptide synthesis.
- Toxicity: Gastrointestinal (nausea, vomiting, diarrhea) > allergic manifestations > CNS:
 - Allergy: 5% manifest penicillin sensitivities = local pruritus, asthma; 1% develop anaphylaxis. Treatment: O_2 , epinephrine-nor-epinephrine, β_2 -agonists, steroids, H_1 - and H_2 -blockers, theophylline, fluids. Consider glucagon for severe hypotension.
 - CNS: Seizures due to inhibition of GABA-to-receptor binding. Treatment: benzodiazepines > barbiturates.

Unique Toxicities

- Jarisch-Herxheimer reaction: Acute febrile response to antigens released from lysed spirochetes = myalgias, chills, fever, headache, rash.
- Hoigne syndrome: Local anesthetic toxicity reaction due to the procaine contained in procaine-penicillin G = seizures, hallucinations, tachycardia, and hypertension.
- Hyperkalemia: Due to potassium-penicillin G administration in chronic renal failure (CRF) patients.

Cephalosporins

Mechanism and Toxicity

- Mechanism: β -lactams, like penicillins, that interfere with bacterial cell wall integrity.
- Toxicity: Allergy > hematological manifestations:
 - Allergy: 4% in general population, but increases to 8% in those with a preexisting penicillin allergy.
 - Hematological: Acute hemolysis.
- Acute overdose: Same as penicillin, but not as life-threatening.

Unique Toxicities

- n-Methylthiotetrazole (nMTT) side-chain reactions: Disulfiram-like reactions due to inhibition of aldehyde dehydrogenase = nausea, vomiting, and flushing following ethanol consumption.
- n-MTT-mediated hypoprothrombinemia: Due to inhibition of active vitamin K formation.
- n-MTT representatives: Cefazolin, cefotetan, cefamandole, moxalactam.

Aminoglycosides

Mechanism and Toxicity

- Mechanism: Aminoglycosides inhibit bacterial protein synthesis by blocking 30s RNA ribosomal subunit.
- Representatives: Kanamycin, streptomycin, neomycin, gentamicin, tobramycin, amikacin.
- Toxicity: Ototoxicity > renal toxicity > neuromuscular junction blockade:
 - Ototoxicity: 0.5-5%: (1) cochlear dysfunction = deafness; (2) vestibular toxicity = permanent tinnitus-vertigo from cochlear and vestibular hair cell damage, same as bromates.

Unique Toxicities

- Ototoxicity and vestibular toxicity
- Permanent: (1) Cochlear and (2) vestibular hair cell degeneration (G2):
 - Gentamicin: Causes both cochlear and vestibular that may be permanent ototoxicity
 - Tobramycin: and vestibular ototoxicity that may be permanent
 - Cochlear toxicity alone that may be permanent:
 - Amikacin
 - Kanamycin
 - Neomycin
- Permanent vestibular hair cell degeneration alone

- Streptomycin: Antituberculosis (TB) aminoglycoside
- Nephrotoxicity: Acute tubular necrosis (ATN) possibly during first week of treatment. Unique antidote: ticarcillin — complexes with and binds aminoglycosides to inactivate both antimicrobial and nephrotoxic effects; removes 50% more drug than hemodialysis (HD).
- Neuromuscular blockade: Due to reduced pre-synaptic acetylcholine (ACh) release, especially in those on neuromuscular blockers (NMBs) or with preexisting myasthenia gravis or botulism.

Chloramphenicol

- Mechanism: Inhibits bacterial protein synthesis by blocking 50s ribosomal subunit.
- Toxicity: Cardiovascular and gray baby syndrome > hematological:
 - Cardiovascular: (1) Acute cardiovascular collapse in overdose. Treatment: orogastric lavage, activated charcoal, exchange transfusion in neonates. (2) Gray baby syndrome: hypotension, gray color, vomiting, respiratory distress, hypoglycemia; all due to low hepatic conjugation and reduced renal ability to excrete free drug.
 - Hematological: Dose-dependent bone marrow (BM) suppression and potentially fatal aplastic anemia.

Vancomycin

- Mechanism: Reduced bacterial glycopeptide polymerization with cell wall instability.
- Toxicity: Dermatitis/allergy > renal > hematological:
 - Dermal: 3.4% will develop red man syndrome, a glycopeptide-induced anaphylactoid reaction with pruritus–urticaria–angioedema, hypotension, angina, cardiovascular collapse, seizures.
 - Treatment: slow IV administration, H₁-blockers.
 - Renal: Nephrotoxicity due to chronic use.
 - Hemotoxicity: Rarely neutropenia and thrombocytopenia.

Fluoroquinolones

- Representatives: Ciprofloxacin, ofloxacin, norfloxacin, levofloxacin.
- Mechanism: Quinolones inhibit bacterial DNA replication.
- Toxicity: Soft tissue > CNS > renal:
 - Soft tissue: Target and damage developing articular cartilage, especially in children and pregnancy.
 - CNS: Rarely, seizures due to GABA inhibition, especially during concomitant theophylline treatment.
 - Renal: Rarely, renal failure.

Macrolides

- Mechanism: Macrolides reduce bacterial protein synthesis by inhibiting 50s RNS ribosomal subunit.
- Representatives: Erythromycin estolate-lactobionate-stearate, clarithromycin, azithromycin.
- Toxicity: Cardiovascular > drug–drug interactions > hepatotoxicity > ototoxicity:
 - Cardiovascular: Lactobionate causes prolonged QT and torsades due to K-channel block.
 - Drug–drug interactions: Erythromycins inhibit P-450 = torsades when co-administered with the nonsedating antihistamines, astemizole or terfenadine.
 - Hepatic: Estolate causes cholestatic hepatitis with chronic use.
 - Ototoxicity: Reversible high-frequency hearing loss.

Sulfonamides

- Mechanism: Sulfonamides inhibit bacterial *para*-aminobenzoic acid (PABA) metabolism required for folic acid synthesis.
- Toxicity: Gastrointestinal (nausea and vomiting) > dermal > hematological > renal > metabolic:
 - Dermal: Skin hypersensitivity.
 - Hematological: BM suppression and aplastic anemia, especially with folic acid or B₁₂ deficiency.
 - Renal: Nephrolithiasis.
 - Metabolic: Hypoglycemia.

- CRANK: Crystalluria, rash, aplastic anemia, nausea, kernicterus (neonatal jaundice).

Tetracyclines

- Mechanism: Tetracyclines reduce bacterial protein synthesis by binding to the 30s RNA ribosomal subunits.
- Representatives: Tetracycline, oxytetracycline, doxycycline, minocycline.
- Toxicity: Dermal > bone > gastrointestinal:
 - Dermal: Sun-exposed skin develops hypersensitivity and hyperpigmentation.
 - Bone: Discolors teeth in children <6–8 years old and in fetuses >12 weeks.
 - Gastrointestinal: Nausea, vomiting, epigastric pain, esophageal ulceration.

Antifungals

Amphotericin B

- Mechanism: Combines with ergosterol in the fungal cytoplasmic cell membrane to reduce cell wall integrity and increase porosity with leakage of cellular organelles.
- Toxicity: Febrile syndrome > renal > hematological:

- Febrile Syndrome: Fever, headache, rigors, nausea, vomiting, dyspnea, hypotension and bradycardia, IV phlebitis. Pretreatment: acetaminophen (APAP), steroids, H₁-blockers.
- Renal: 80% develop minor renal insufficiency; later azotemia possible due to renal tubular damage and renal artery vasoconstriction.
- Hematological: BM suppression = aplastic anemia, leukopenia, thrombocytopenia.

Azoles

- Mechanism: Azoles alter fungal cell membranes to increase permeability.
- Representatives:
 - Triazoles: Fluconazole, itraconazole.
 - Imidazoles: Miconazole, clotrimazole.
- Toxicity: Increased drug–drug interactions:
 - Drug–drug interactions: Azoles inhibit CYP3A4, responsible for metabolizing many drugs, including statins, H₁-blockers, steroids, benzodiazepines, calcium channel blockers (CCBs).

Antituberculous Agent Toxicity

TB and Isoniazid (INH) Epidemiology

- TB is epidemic among high-risk populations of Asian, African, and Eastern European immigrants; Native Americans and Inuits; alcoholics; prisoners; homeless; refugees; intravenous drug users (IVDUs), and HIV/AIDS patients.
- Approximately 2 billion people worldwide are infected with TB, with 10 million new cases per year, and 1 million deaths per year.
- Isonicotinyl hydrazide (INH) or isoniazid is among the most common causes of drug-induced seizures in the United States.
- 10–20% of patients taking INH will develop asymptomatic high ALT and AST (2–3 times normal serum levels); 10% of these will develop INH hepatitis (1% total) with a 10% case fatality rate (CFR = 0.1).
- INH toxic risk factors: rapid acetylators of INH; the elderly or malnourished; alcoholics; patients with preexisting liver disease; synergistic drug toxicity: INH and concomitant rifampin or pyrazinamide antituberculosis treatment.

INH Pharmacokinetics

INH Pharmacology

- Absorption: Rapid following oral ingestion from gastrointestinal tract, peak levels in 1–2 hours.
- Very low V_d : 0.6 L/kg.
- Low protein binding: 10%.
- Mostly renally excreted: 75–95%.
- Easily dialyzable: Due to low V_d , reduced protein binding, and increased renal excretion.

INH Metabolism

- Hepatic metabolism: Two pathways, (1) acetylation > (2) dehydrazination.
- Rapid acetylators of INH: An autosomal dominant trait present in 50% of U.S. population and 95% of Inuits, Chinese, Japanese, and Africans — who will distribute 30–50% less free INH than slow acetylators (most whites) with reduced half-life and less drug efficacy. Slow acetylators = higher INH toxicity, especially slow acetylators on concomitant rifampin.
- Who are the slow acetylators? 60% of Caucasian Americans, 60% of Jews, 50% of African Americans — all groups are at greater risk of INH toxicity.

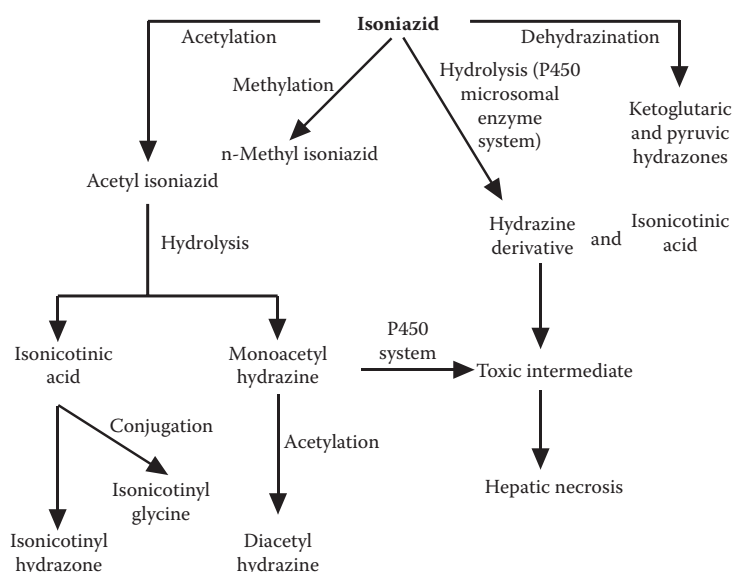


FIGURE 11.1 Isoniazid (INH) metabolism. The intrahepatic biotransformation pathways of isoniazid (INH) and the production of non-toxic and toxic intermediate metabolites.

INH Mechanisms and Toxicity

INH Mechanisms

- Pyridoxine (or B₆ = cofactor for GABA synthesis) antagonism via three mechanisms:
 - B₆ complex: INH complexes directly with B₆ to form a large complex, not activated and excreted in urine.
 - INH hydrazones: Dehydrazination produces hydrazone metabolites that inhibit pyridoxine phosphokinase, the enzyme catalyzing activation of B₆ to active form, pyridoxyl-5'-phosphate.
 - INH inhibits pyridoxyl phosphate: The active form of B₆ and the final required cofactor for the synthesis of the inhibitory neurotransmitter, GABA = reduced CNS GABA levels = seizures.

INH Toxicity

- Acute toxicity: CNS > metabolic > gastrointestinal
- INH triad = (1) refractory seizures, (2) metabolic acidosis (really lactic acidosis because INH also inhibits the metabolism of lactate to pyruvate), and (3) persistent coma.
- Initial gastrointestinal: Nausea and vomiting; then dizziness, hyperthermia, and hypotension.
- CNS: Tonic-clonic seizure, refractory status epilepticus (CFR 20%).
- Metabolic: High anion gap metabolic acidosis mimicking diabetic ketoacidosis due to seizures and increased lactate levels.
- Toxic doses: Seizures >20 mg/kg; death >50 mg/kg; LD₅₀ >80–150 mg/kg.

INH Overdose Management

General Management of INH Overdose

- No ipecac: Due to unprotected airway during seizures, airway loss, and aspiration risk.
- Secure airway: Endotracheal intubation; insert orogastric.
- Immediate orogastric lavage: Then AC and cathartic.
- Multi-dose activated charcoal (MDAC): No additional cathartic.

- Sodium bicarbonate (NaHCO₃): Correct metabolic acidosis.
- Dialysis: Reserve hemodialysis (HD) and hemoperfusion (HP) for those with renal insufficiency.

Specific Management of INH Overdose

- Pyridoxine (B₆): For seizure control; use 1 g per gram of INH ingested, to a maximum of 5 g at 1 g every 2–3 minutes.
- Repeat pyridoxine: For refractory seizures and status epilepticus.
- Add diazepam: Diazepam and pyridoxine (B₆) act synergistically to enhance GABA's seizure-inhibition activity.

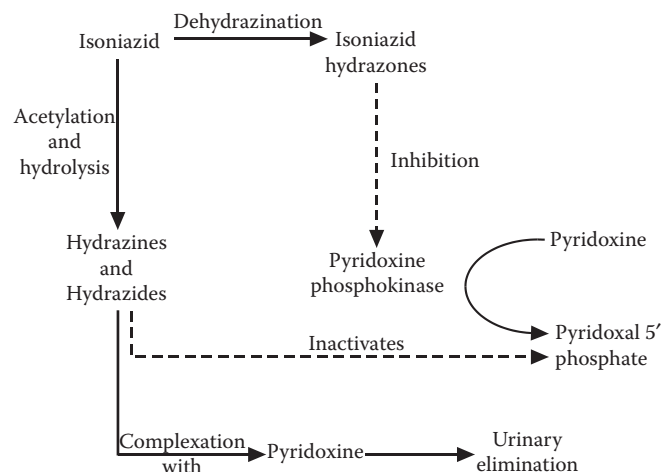


FIGURE 11.2 Isoniazid (INH) toxicity 1. The mechanisms and sites of action of isoniazid (INH)-mediated epileptogenic neurotoxicity.

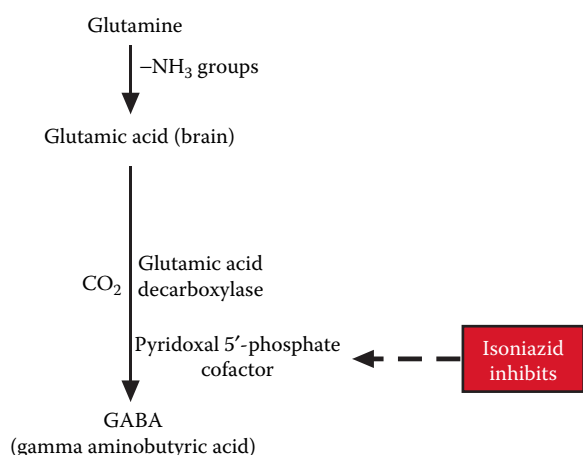


FIGURE 11.3 Isoniazid (INH) toxicity 2. Additional mechanisms and sites of action of isoniazid (INH)-mediated epileptogenic neurotoxicity.

Chronic INH Toxicity

Common Side Effects: #1 Hepatic

- Adverse reactions: 5.4% will develop fever, rash, peripheral and/or optic neuritis, or jaundice.
- Liver function tests: 10% develop asymptomatic hepatitis with high liver function tests.
- INH hepatitis: 1% will develop nausea, vomiting, fever, fatigue, RUQ pain due to hydrazine intermediates that covalently bind to hepatocytes; hepatic necrosis, may occur, especially in slow acetylators also taking rifampin (APAP-like mechanism of toxicity).

Less Common Side Effects: #1 CNS

- Optic neuritis: INH can cause optic neuritis and optic atrophy.
- Peripheral neuropathy: Up to 20% of patients on INH therapy may develop distal sensory and motor axonopathy.
- Pellagra-like skin syndrome: Triad of dermatitis, diarrhea, and dementia due to inability of pyridoxyl-5'-phosphate to serve as a required cofactor in niacin synthesis = niacin deficiency results in pellagra, the 3-D syndrome.

Other AntiTuberculosis Agents

Rifampin

- Mechanism: Special antibiotic that inhibits bacterial DNA-dependent RNA polymerase.
- Pharmacology: Well absorbed orally, peaks IV 2–4 hours, high V_d (1.6 L/kg), 75% protein bound, enterohepatic recirculation, 30% excreted, potent P-450 inducer.
- Toxicity: 6% gastrointestinal (nausea, vomiting) > dermal > hepatic:
 - Dermal toxicity: red-orange staining of skin, fluids (urine, tears, sweat, breast milk) and tissues, flushing, rash, pruritus.
 - Hepatic: 33% manifest increased liver function tests (LFTs) and 1% will develop hepatitis with jaundice, especially in slow rifampin inactivators, patients with history of liver disease, and patients on INH co-treatment.
- Treatment: Orogastic lavage, AC, MDAC, hemodialysis — hemoperfusion (HD-HP) ineffective.

Ethambutol

- Mechanism: Antimetabolite that inhibits bacterial RNA synthesis.
- Pharmacology: Well absorbed orally, peaks IV 2–4 hours, 20% metabolized, 50% excreted.
- Toxicity: Eye > initial gastrointestinal and CNS > metabolic:
 - Ocular: Optic neuritis, reduced visual acuity, reduced red-green color perception; all dose-related and reversible.
 - Gastrointestinal, then CNS: Initial nausea and crampy pain, then confusion and hallucinations.
 - Metabolic: Inhibits renal uric acid excretion and causes acute gout.

Pyrazinamide

- Mechanism: Bactericidal analog of nicotinic acid.
- Pharmacology: Well absorbed orally, peaks in 2 hours, partially metabolized, excreted by filtration.
- Toxicity: Hepatic > metabolic:
 - Hepatic: 15% will develop acute hepatitis with CFR 2–3% due to acute hepatic necrosis.
 - Metabolic: Inhibits renal uric acid excretion and causes acute gout.

Streptomycin

- Mechanism: An aminoglycoside antibiotic that inhibits bacterial protein synthesis by binding to 30s subunit of bacterial ribosomal RNA.
- Pharmacology: Intramuscular (IM) administration only, peaks in 1 hour, 34% protein bound, half-life of 2–5 hours, 89% excreted.
- Toxicity: Ototoxicity > neuromuscular junction blockade > hemotoxicity > renal:
 - Ototoxicity: Tinnitus, vertigo, dizziness, ataxia, deafness, congenital CN VIII damage.
 - Neuromuscular block: Reduces presynaptic Ach release; reversed by calcium, not neostigmine.
 - Hemotoxicity: Hemolytic anemia, IgG-mediated factor V inhibition with bleeding.
 - Renal: Aminoglycoside nephrotoxicity; no hepatotoxicity.

Antimalarial Agent Toxicity

Current Antimalarials

- Quinolines: Quinine, quinidine, chloroquine, primaquine.
- Dihydrofolate reductase inhibitors (folic acid inhibitors): Proguanil, pyrimethamine, pyrimethamine + dapsone (Maloprim®), pyrimethamine + sulfadoxine (Fansidar®).
- Sulfonamides/sulfones: Sulfonamides — sulfadoxine/sulfones — dapsone.
- Antibiotics: Tetracycline, doxycycline, azithromycin.
- Miscellaneous: Halofantrin, artemisinins.

Quinine and Cinchonism

Pharmacology: Quinine and Quinidine

- Source: The optical isomers, quinine and quinidine, are extracts from the bark (Jesuit bark) of the South African *Cinchona* tree.
- Absorption: Rapid and complete orally, peaks in 3 hours.
- Protein binding: 95%.
- V_d : 1.8 L/kg.
- Half-life: 6–8 hours.
- Metabolism: 80%.
- Renal excretion: 20%.

Cinchonism

- Toxicity: CNS > gastrointestinal > dermatological > hematological:
 - CNS: Headache, dizzy-vertigo, confusion, syncope, delirium, seizures, coma.
 - Eye: Mydriasis, scotomata, diplopia, blurred vision, photophobia, visual field cuts, reduced color vision.
 - Ototoxicity: Tinnitus, deafness.
 - Cardiovascular: A Class IA antiarrhythmic = prolonged PR-QRS-QT; torsades de pointes, ventricular tachycardia, ventricular fibrillation, vasodilation, then hypotension.

- Gastrointestinal/endocrine: Increased nausea and vomiting, increased insulin release — hypoglycemia (similar to sulfonylureas).
- Dermatology: Flushing, rash, angioedema.
- Hemotoxicity: Hemolysis in G-6-PD deficiency, thrombocytopenia.
- Miscellaneous: Oxytocic properties may precipitate premature labor.

Quinine and Quinidine Overdose

General Overdose Management

- No ipecac: Due to emesis, seizures, aspiration risks.
- Orogastric lavage: Only for ingestions of <1 hour.
- AC + cathartic: 1 g/kg.
- MDAC: 0.5 g/kg, no cathartic, every 2–4 hours.

Specific Overdose Management

- Serum alkalinization to pH 7.45–7.50, especially for widened QRS complex with myocardial depression.
- Avoid IA and IC antidysrhythmics with quinine/quinidine additive toxicities.
- Large V_d renders HP and HD ineffective.
- Eye: Monitor for retinal toxicity with baseline fundoscopy, visual fields, and color testing.

Chloroquine Toxicity

Chloroquine Pharmacology and Mechanisms

- Epidemiology: Highest overdose case fatality rate (CFR) of all antimalarials; narrow therapeutic index.
- Pharmacology: Rapidly absorbed orally, peaks in 1–3 hours, highly protein bound 70%, very long half-life (40+ days), not dialyzable.

- Binds to tissues: Liver, lungs, kidneys.
- Less ocular toxicity than quinine/quinidine.

Chloroquine Toxicity and Management

- Toxicity: Cardiovascular and CNS > pulmonary > metabolic:
 - Cardiovascular: Wide QRS, peripheral vasodilation, direct myocardial depression, severe hypotension, cardiovascular collapse.
 - CNS: CNS depression, headache, dizziness, seizures.
 - Pulmonary: Respiratory depression and sudden apnea possible.
 - Metabolic: Severe hypokalemia, flattened T waves, U waves, shortened ST segments.
- Management: Combined epinephrine and diazepam = best overdose management combination.

Other Antimalarials

Mefloquine

- Use: Chloroquine-resistant *Plasmodium falciparum*.
- Pharmacology: Long half-life of 20 days.
- Toxicity: CNS > cardiovascular > hepatic:
 - CNS: Hallucinations, nightmares, seizures, diffuse encephalopathy.
 - Cardiovascular: Hypotension, dysrhythmias.

Primaquine

- Uses: Relapsing malaria due to *P. vivax* and *P. ovale*.
- Toxicity: Less CNS toxicity than mefloquine.
- Methemoglobinemia: Especially in G-6-PD deficient patients.

Cancer Chemotherapeutics: Outline

Human Carcinogens

Classification

Epidemiology

Methotrexate (MTX)

- MTX mechanisms, indications, and toxicities
- General management of MTX overdose
- Specific management of MTX overdose
- General management of intrathecal MTX overdose
- Specific management of intrathecal MTX overdose

Vincristine (VCR)

- VCR mechanisms, indications, and toxicities
- General management of VCR overdose
- Specific management of VCR overdose
- VCR intrathecal overdose and VCR extravasation

Anthracycline\Antibiotics

- Antibiotic toxicities
- Anthracycline extravasation

Nitrogen Mustards

- Toxicities and management
- Mustard extravasation

Platinoids

- Platinoid mechanism and toxicity
- Platinoid overdose management

Human Carcinogens

Alkylating chemotherapy agents: Cyclophosphamide, melphalan.

Aromatics: Aromatic amines, benzene, benzidine, polycyclic aromatic hydrocarbons (PAHs).

Environmental toxins: Aflatoxins, tobacco smoke, tars, soots, hydrocarbon, dry cleaning and degreasing solvents = carbon tetrachloride (CCl_4), perchloroethylene, trichloroethylene, trichloroethane.

Hormones: Estrogens (diethyl stilbesterol), anabolic steroids.

Plastics: Vinyl chloride monomer, aryl acrylates.

Heavy metals: Arsenic, chromium, nickel.

Ionizing radiation: Radon, x-rays.

Nonionizing radiation: Ultraviolet light.

Miscellaneous drugs: Chloramphenicol, phenytoin.

Industrial exposures: Arsenic, asbestos, cadmium, chromium, nickel, silica.

Classification

- Antimetabolites: Example = methotrexate (MTX), a dihydrofolate reductase (DHFR) and thymidine synthetase inhibitor that prevents activated, reduced folate from serving as a cofactor for DNA and RNA synthesis. Overdose causes diffuse mucositis, myelosuppression, acute renal failure, and death, usually from sepsis.
- Antimitotics: Examples = vincristine (VCR) and vinblastine (VB), both vinca plant alkaloids that inhibit microtubular polymerization and arrest mitosis at metaphase, limiting cell movement and cell division. Overdoses cause seizures, encephalopathy, autonomic dysfunction, myelosuppression, and inappropriate secretion of antidiuretic hormone.
- Antibiotics: Two main classes = (1) the true anthracyclines = daunorubicin, doxorubicin, and (2) the mycins = adriamycin, bleomycin, mithramycin, mitomycin. Most antineoplastic antibiotics are derived from the *Streptomyces* bacterium and release oxygen (O⁻) free radicals (similar to paraquat), causing severe cardiotoxicity, parenchymal pulmonary toxicity, mucositis, and myelosuppression.
- Alkylating agents: Two main classes = (1) nitrogen mustards, like cyclophosphamide and chlorambucil, can cause hemorrhagic cystitis and myelosuppression on overdose; and (2) heavy metal platinoids, like cisplatin and carboplatin, can cause seizures, encephalopathy, retinal toxicity, ototoxicity, and peripheral neuropathy on overdose.

TABLE 11.1 Classification of Anti-Cancer Agents and Their Toxicities

Class	Agent	Toxicity	Overdose	Antidote
Alkylating agents	Mustards Chlorambucil Cyclophosphamide	Hemorrhagic cystitis, encephalopathy, pulmonary fibrosis	Seizures, myocardial necrosis	Benzodiazepines
	Platinoids Cisplatin Carboplatin	Peripheral neuropathy, ototoxicity, retinal toxicity, distal tubular necrosis, acute renal failure, myelosuppression	Seizures, encephalopathy, ototoxicity, renal toxicity	Diethyldithiocarbamate (chelates platinum)
Antimetabolites	Methotrexate	Mucosities, acute renal failure, elevated transaminases	Myelosuppression	Folinic acid (to block DHFR inhibition)
Antimitotics	Vinblastine Vincristine	Peripheral neuropathy, autonomic neuropathy	Seizures, encephalopathy, paralytic ileus, myelosuppression, SIADH	Glutamic acid (to stabilize tubulin)
Antibiotics	Anthracyclines Doxorubicin	Direct cardiotoxicity, congestive cardiomyopathy	Dysrhythmias, congestive heart failure	Digoxin
	Mycins Mithramycin	Pulmonary fibrosis	Respiratory failure	None, avoid high FO ₂

Note: DHFR = dihydrofolate reductase; SIADH = syndrome of inappropriate secretion of antidiuretic hormone.

Epidemiology

- Antineoplastic agents have a very narrow therapeutic index; 90% of overdoses are unintentional and iatrogenic; and 20% result in moderate-to-severe toxicity.
- Antineoplastic agent overdose has increased threefold over the past 10 years.
- Vincristine overdose is the most frequently reported antineoplastic agent overdose.
- Anthracycline and mycin antibiotics (doxorubicin, bleomycin) are the most toxic cancer chemotherapeutics and can cause oxygen-free-radical-induced cardiomyopathy with irreversible congestive heart failure (CHF) and a high case fatality rate (CFR) of 48%+.

Methotrexate (MTX)

MTX Mechanisms, Indications, and Toxicities

- Mechanisms: Inhibits both dihydrofolate reductase (DHFR) and thymidine (thymidylate) synthetase, making reduced folate (folic acid) unavailable for DNA and RNA synthesis.
- Indications: Lymphoma, lymphocytic leukemia, breast cancer, small cell carcinomas, gestational trophoblastic disease, rheumatoid arthritis, psoriasis, suppression of organ transplant rejection.
- Toxicities: Gastrointestinal > renal > bone marrow > CNS > pulmonary:
 - Gastrointestinal: Nausea, vomiting, mucositis = stomatitis, esophagitis, diarrhea; hepatotoxicity = increased hepatic transaminases (AST/ALT).
 - Renal: Oliguria and azotemia = acute renal failure.
 - Bone marrow: Pancytopenia.
 - CNS: Seizures, hemiparesis.
 - Pulmonary: Delayed (by 12–17 years) hypersensitivity pneumonitis.

➤ MTX inhibits both dihydrofolate reductase & thymidylate synthetase

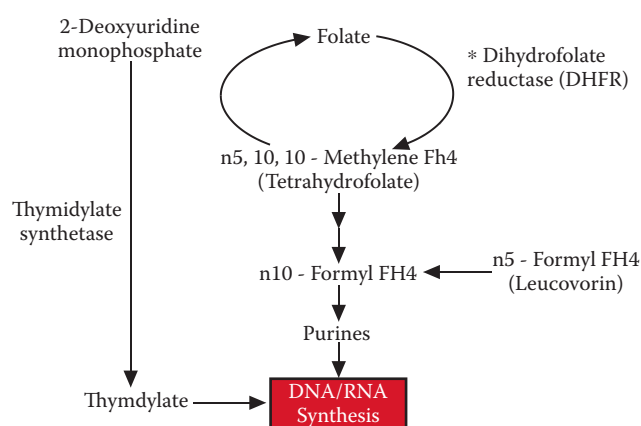


FIGURE 11.4 The mechanisms of action of methotrexate (MTX). The anti-neoplastic activities and sites of action of the commonly prescribed cancer chemotherapeutic agent, methotrexate (MTX).

General Management of MTX Overdose

- Immediate gastric emptying: Ipecac only if witnessed ingestion.
- Orogastric lavage: Then AC, no cathartic.
- MDAC: No cathartic.
- Cholestyramine: Synergistic with MDAC in interrupting enterohepatic circulation of MTX.
- Fluid loading: For diuresis.
- Urinary alkalization: Using intravenous sodium bicarbonate (NaHCO_3) to maintain urine at pH 7–8.

Specific Management of MTX Overdose

- Antidote: Leucovorin (folinic acid) — restores reduced folate; monitor efficacy of folinic acid therapy with decreasing MTX levels. Folic acid is ineffective as a specific antidote; only folinic acid is effective.
- Enhanced elimination: Hemoperfusion (HP) best: HP > HP and hemodialysis (HD) > HD (removes both folic and folinic acids).
- Specific granulocyte colony stimulating factors (G-CSF): For bone marrow suppression with pancytopenia; will restore granulocytes and reduce risk of sepsis.

General Management of Intrathecal MTX Overdose

- Maintain upright, sitting posture.
- Spinal tap for cerebrospinal fluid (CSF) drainage: Use same lumbar puncture (LP) site, if possible.
- Perform CSF exchange: 2–3 exchanges replacing CSF with equal parts (30 mL) of lactated Ringer's solution (LR) to CSF.
- Consider CSF perfusion: Perform ventriculostomy for spinal subarachnoid space irrigation with LR and 25 mL fresh frozen plasma (FFP)/L of LR at 150 mL/hour for 24 hours.

Specific Management of Intrathecal MTX Overdose

- High dose leucovorin (folinic acid) rescue: IV only; CNS toxic if given intrathecally (IT).
- Overhydration: To promote renal excretion.
- Urinary alkalinization.
- Dexamethasone IV: To limit meningeal inflammation.

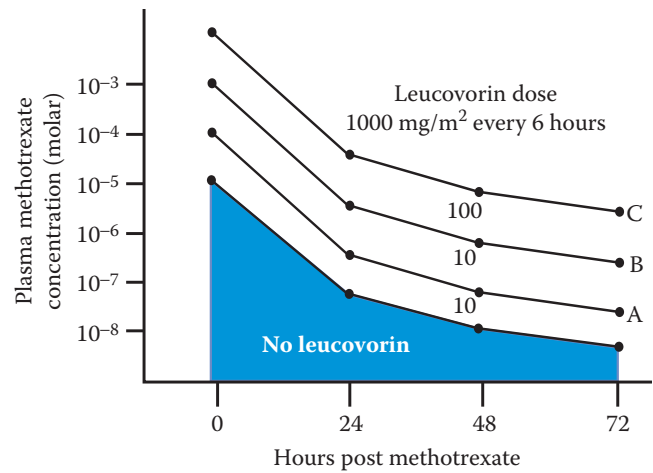


FIGURE 11.5 The management of methotrexate (MTX) overdose with leucovorin. A clearance graph of the efficacy of leucovorin in the management of methotrexate (MTX) overdose.

Vincristine (VCR)

VCR Mechanisms, Indications, and Toxicities

- Mechanisms: VCR and vinblastine (VB) are periwinkle plant alkaloids that, like colchicine (from crocus plants) and podophyllin from mayapple plant, bind to tubulin to prevent its polymerization into microtubules, arresting mitosis at metaphase, and inhibiting cell movements and cell division.
- Indications: Leukemias, lymphomas, solid tumors.
- Toxicities: CNS > bone marrow > cardiovascular:
 - CNS: ascending peripheral neuropathy (axonopathy), seizures, encephalopathy, autonomic dysfunction = paralytic ileus, atonic bladder; hypothalamic stimulation = fever and syndrome of inappropriate antidiuretic hormone secretion (SIADH) with hyponatremia and intravascular volume overloading.
 - Bone marrow: Myelosuppression, VB > VCR.
 - Cardiovascular: Necrotic myocardial infarction as a result of alkaloid-induced coronary vasospasm and platelet aggregation.

General Management of VCR Overdose

- Oral overdose: Ipecac only if witnessed ingestion, then orogastric lavage and AC.
- IV overdose: Most common, provide seizure management with benzodiazepines (BZs) preferred over barbiturates (respiratory and cardiovascular depressants), secure airway immediately.

Specific Management of VCR Overdose

- Antidote = Glutamic acid: May assist in stabilization of tubulin promoting polymerization into microtubules, restoring granulocyte locomotion and propagation, and improving peripheral neuropathy.

tion and propagation, and improving peripheral neuropathy.

- Leucovorin (folinic acid): May limit neuropathy and myelosuppression by blocking VCR's inhibition of both DHFR and thymidylate synthetase.

VCR Intrathecal Overdose and Extravasation

Intrathecal Overdose of VCR

- High CFR: Secondary to chemical arachnoiditis, ascending neuropathy, encephalopathy, and seizures.
- Posture: Maintain upright for gravitational protection of brain.
- CSF drainage: Use same LP.
- CSF exchange: 30 mL lactated Ringer's solution per 30 mL CSF every 3 exchanges.
- CSF perfusion: Lactated Ringer's solution + FFP 25 mL/L as for intrathecal overdose of MTX.

VCR Subcutaneous Extravasation

- Aspirate infusate: From infiltrated IV site.
- Consider dilution: Use normal saline to dilute VCR in subcutaneous tissues.
- Hyaluronidase: Inject intradermally or subcutaneously to promote systemic absorption of VCR.
- Warm dry compresses: To promote vasodilation and systemic absorption of VCR.
- Extremity elevation: To limit further progression of extravasation.

Anthracyclines/Antibiotics

Antibiotic Toxicities

- Representatives: (1) Doxorubicin group, including all *Streptomyces*-derived antibiotics, are cardiotoxic (increased risk of CHF) free radical formers; (2) mycins: adriamycin, bleomycin, mitomycin.
- Antidotes: None.
- Cardiotoxicity: Monitor for 10% drop in ejection fraction.
- Cardioprotectants: Consider digoxin to increase ejection fraction.
- Pulmonary toxicity: Maintain adequate oxygen saturation with the lowest inspired concentrations of oxygen to limit oxygen toxicity with enhanced pulmonary parenchymal damage.
- Myelosuppression: Monitor CBC and platelets.
- Enhanced elimination: Hemoperfusion (HP) only.

Anthracycline Extravasation

- Consider dimethylsulfoxide (DMSO) as a free radical scavenger.
- Cold compresses to reduce swelling and limit absorption.
- Extremity elevation.

Nitrogen Mustards

Toxicities and Management

- Representatives: Cyclophosphamide, chlorambucil, mechlorethamine.
- Mechanism: Form reactive intermediates that bind to nucleophilic moieties on DNA.
- Toxicities: Chlorambucil — seizures, CNS depression; cyclophosphamide — hemorrhagic cystitis in 10% of cases and cardiotoxicity = arrhythmias and myocarditis.
- Management: Benzodiazepines (BZs) for seizures, secure the airway, orogastric lavage, activated charcoal (AC).

Mustard Extravasation

- Sodium thiosulfate: Administer intradermally or subcutaneously to dilute extravasation and inhibit subcutaneous tissue alkylation by blistering mustards through sulfhydryl group donation.
- Cool compresses.
- Extremity elevation.

Platinoids

Platinoid Mechanism and Toxicity

- Representatives: Platinum-containing cisplatin and carboplatin.
- Mechanism: Platinoids form intra- and inter-strand crosslinks with DNA molecules when hydrolytically activated upon entering low chloride intracellular environments.
- Toxicities: CNS > renal > bone marrow:
 - CNS: Seizures, encephalopathy, heavy-metal induced sensory peripheral neuropathy-axonopathy, retinal toxicity, reduced color vision, ototoxicity (high-frequency).
 - Renal: Distal tubular necrosis with subsequent acute renal failure (ARF).
 - Bone marrow: Myelosuppression: anemia, thrombocytopenia.

Platinoid Overdose Management

- Renal protection: By (1) chloride diuresis — intravenous administration of 0.9% NaCl + mannitol to maintain high chloride (Cl) diuresis and increased platinum excretion; and (2) nephroprotection with two specific antidotes: diethyldithiocarbamate (DDTC) or its precursor disulfiram and sodium thiosulfate, both of which chelate free platinum.
- Enhanced elimination: Plasmapheresis only, especially for chelated platinum; HD ineffective.

Part 3:

Hypoglycemics: Outline

Definitions

Epidemiology

Etiologies of hypoglycemia

Clinical manifestations of hypoglycemia

Orally administered hypoglycemic agents

**General and specific management
of toxic hypoglycemia**

Surreptitious hypoglycemia

Definitions

- Hypoglycemia: Failure to maintain serum glucose >60 mg/dL.
- Euglycemia: Serum glucose level of 70–110 mg/dL.
- Therapeutic euglycemia maintenance: 100–250 mg/dL.

Epidemiology

- Accidental insulin overdose: Most common cause of hypoglycemia due to combinations of insulin dose miscalculations, reduced caloric intake, increased exercise level or intercurrent infections or other illnesses.
- Long-acting (LA) sulfonylureas: Most common cause of non-insulin, drug-induced hypoglycemia, especially chlorpropamide LA and glyburide LA.
- Market withdrawals: (1) The biguanide, phenformin, was withdrawn in 1976, due to fatal lactic acidosis; (2) troglitazone (Rezulin®), a thiazolidinedione, was withdrawn in the 1990s, due to fatal hepatotoxicity.

Etiologies of Hypoglycemia

- Pathophysiological: Endocrinopathy (Addison's disease, Sheehan's syndrome); neoplasms (insulinomas, multiple endocrine adenomatosis [MEA] type I); liver disease (alcoholism, cirrhosis); chronic renal failure (CRF) and hemodialysis; miscellaneous (AIDS, autoimmune diseases, pregnancy).
- Drug-induced: Oral hypoglycemic agents, parenteral insulin preparations.
- Food or drug potentiation of hypoglycemic agents: Foods (unripe Jamaican ackee fruit-hypoglycin [vomiting, hypoglycemia, CNS depression, seizures], ethanol); drugs (ACE inhibitors, β -blockers, chloramphenicol, disopyramide, MAOIs, quinine-quinidine, salicylates, sulfonamides).

Clinical Manifestations of Hypoglycemia

Manifestations Caused by Catecholamine Release

- Cardiovascular effects: Arrhythmias (SVT, PVCs, atrial fibrillation); hypertension — headache; angina from cardiac ischemia, myocardial infarction.
- Autonomic effects: Anxiety, diaphoresis, dry mouth, pallor, piloerection.
- Gastrointestinal effects: Hunger, nausea.

Manifestations Due to Cerebral Glucose Depletion

- Acute delirium: Confusion, bizarre behavior, mania.
- Coma: Posturing, CNS and respiratory depression, hypothermia, preserved brainstem reflexes (doll's eyes, oculocephalic, oculovestibular, and papillary light reflexes).
- Focal neurologic deficits: Mimics cerebrovascular accident (CVA) or stroke, ataxia, weakness, hemiparesis, hemiplegia.
- Solitary or refractory seizures: No postictal periods.

Orally Administered Hypoglycemic Agents

Sulfonylureas

- First- vs. second-generation sulfonylureas are derivatives of the sulfonamide antibiotics that stimulate insulin release from pancreatic beta islet cells by blocking K channels and opening Na channels to cause depolarization and release of endogenous insulin. Sulfonamides also decrease hepatic gluconeogenesis and increase peripheral tissue sensitivity to insulin.

Intestinal Alpha-Glucosidase inhibitor

- Acarbose (Precose®); reduces sugar absorption from gut, does not cause hypoglycemia, must be used concomitantly with sulfonylureas.

Thiazolidinediones

- Troglitazone (Rezulin®); recently withdrawn due to fatal hepatotoxicity.

First generation: Few hypoglycemic events, but can act up to 72 hours

- Acetohexamide (Dymelor®)
- Chlorpropamide (Diabenese®), long-acting (LA)
- Tolazamide (Tolinase®)
- Tolbutamide (Orinase®)

Second generation: All LA preparations increase hypoglycemic events

- Glipizide (Glucotrol®) LA
- Glyburide (Diabeta®, Micronase®) LA

Mechanisms: Sulfonylureas stimulate pancreatic beta cells to release preformed endogenous insulin

- Type I IDDM: Ineffective.
- Type II NIDDM: Effective.
- Non-diabetics: Can cause severe hypoglycemia, especially long-acting chlorpropamide and all second-generation sulfonylureas, glipizide and glyburide.

Biguanides

Metformin (Glucophage®); phenformin withdrawn in 1976 due to fatal lactic acidosis. The biguanides increase peripheral glucose uptake and decrease hepatic gluconeogenesis.

Mechanism: Biguanides do not stimulate insulin secretion, but do inhibit gluconeogenesis, and promote peripheral tissue, especially muscle tissue, glucose uptake.

- Type I IDDM: Ineffective.
- Type II NIDDM: Effective.
- Non-diabetics: Do not lower blood glucose.

Characteristics of Routinely Administered Insulin Preparations

Table 11.2 Insulin Pharmacokinetics. Common classes and examples of routinely administered insulin preparations that are often mixed on individual daily dosing schedules to permit the most precise therapeutic maintenance of euglycemia in Type I (juvenile diabetes) and Type II (adult-onset diabetes) insulin-dependent diabetics.

Class of Insulin Preparations	Short (rapid)-acting	Intermediate-acting	Long (ultra)-acting
Duration (hours)	3-6	10-18	18-36
Examples of routinely administered insulin preparations	Regular insulin (Humulin®, Novolin®) Insulin aspart (Novolog®) Insulin lispro (Humalog®)	NPH insulin Lente insulin	PZI Ultralente insulin Insulin glargine (Lantus®)
Metabolism	Hepatic	Hepatic	Not metabolized
Excretion	Renal	Renal	Renal excretion only
NPH: Neutral Protamine Hagedorn Insulin. PZI: Protamine Zinc Insulin.			

General and Specific Management of Toxic Hypoglycemia

Immediate General Management

- Contraindicated treatments: No ipecac due to seizures; no glucagon.
- Secure airway: Then left lateral decubitus position.
- Labs: Glucose, BUN-creatinine, electrolytes, Ca, Mg, CBC, ethanol level.
- Coma cocktail: D₅₀W, 1 g/kg, + thiamine, 100 mg.
- Initial orogastric lavage: Then AC and cathartic.
- MDAC: For long-acting (chlorpropamide) and enterohepatic recirculating (glipizide) agents.
- D₁₀W maintenance: Maintain relative euglycemia, 100–250 mg/dL.

Specific Drug Overdose Management

- Urinary alkalinization: Only for chlorpropamide, a weak acid; maintain urine pH 7.0–8.0.
- Diazoxide (Hyperstat®): Directly inhibits insulin secretion from insulinomas and sulfonylurea overdoses; administer 300 mg slow IV over 30 minutes in D₁₀W every 4 hours to avoid hypotension. Diazoxide is a true antidote for sulfonylurea-induced hypoglycemia and blocks insulin release by closing the beta islet cell Na channels, opening their K channels, and stopping beta islet cell depolarization.

- Octreotide (sandostatin): A semisynthetic, long-acting analog of somatostatin that also inhibits insulin release in insulinomas, quinine-quinidine overdoses, and sulfonylurea overdoses (tolbutamide).

Surreptitious Hypoglycemia

Epidemiology

- IDDM patients: High risk for unintentional insulin overdoses.
- Health-care workers: High-risk intentional insulin overdoses; suicides, homicides, child abuse, and elder abuse (Example: Klaus von Bulow case, Newport, RI).

Differential Lab Evaluation

- Insulin induced: High insulin levels, insulin antibodies present, and low C-peptide levels (a useful biomarker of exogenous insulin administration).
- Sulfonylurea induced: High insulin levels, no insulin antibodies, high C-peptide levels, and urinary sulfonylurea metabolites present.

Food Poisonings

Chapter Outline

Introduction

Clinical manifestations

Etiologic agents

Potential etiologic agents
Bioterrorism (BW) agents and categories of BW agents

Top etiologic agents

Bacterial diseases

Bacillus anthracis
Bacillus cereus (d-toxin)
B. Cereus (enterotoxin)
Brucella spp.
Campylobacter jejuni
Clostridium botulinum
Clostridium perfringens
Escherichia coli
Listeria monocytogenes
Salmonella spp.
Shigella sonnei
Staphylococcus aureus
Vibrio cholerae
Non-cholera vibrios
Yersinia enterocolitica

Viral diseases

Hepatitis A virus (HAV)
Hepatitis E virus (HEV)
Norwalk-like viruses
Rotaviruses

Protozoal diseases

Entamoeba histolytica
Giardia lamblia
Coccidial protozoan: *Cryptosporidium parvum*
Coccidial protozoan: *Cyclospora cayatenesis*
Coccidial protozoan: *Isospora belli*
Coccidial protozoan: *Toxoplasma gondii*

Parasitic Diseases

Trichinella spiralis

Cruise Ship Diarrhea

Prevention and control

Conclusions

Final recommendations

Introduction

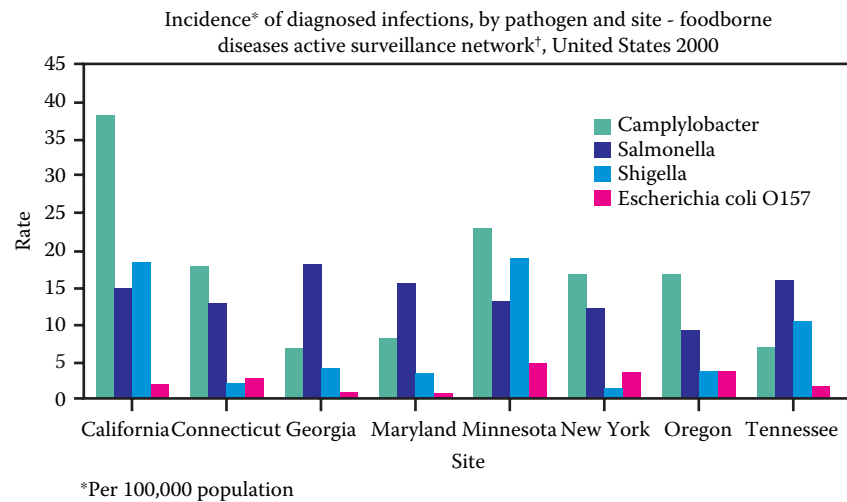


FIGURE 12.1 Active surveillance for foodborne infectious diseases by pathogen and site, U.S., 2002. The incidence of diagnosed foodborne infectious diseases by causative pathogen and state of occurrence in the U.S. in 2002. (Source: U.S. Government Document, CDC, FoodNet, U.S. Foodborne Diseases Active Surveillance Network, 2002.)

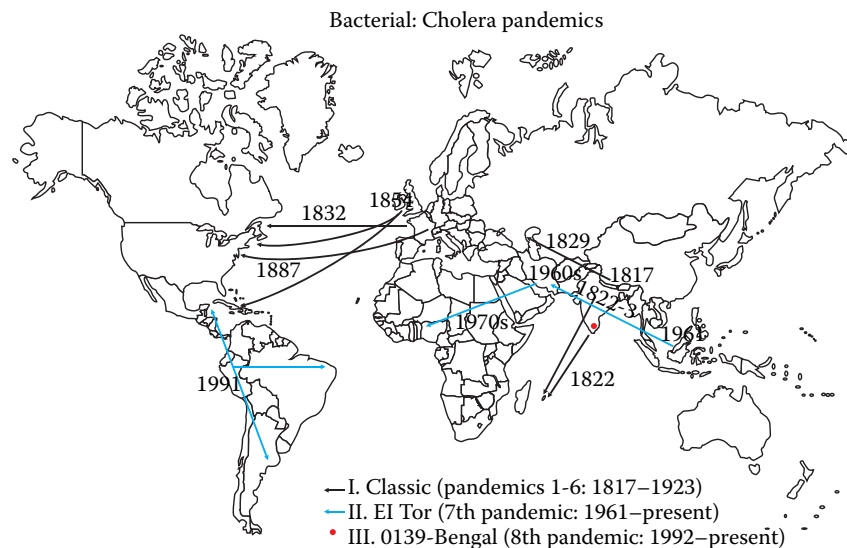


FIGURE 12.2 The historical global cholera pandemics. A world map indicating the major pandemics and the pandemic spreading routes of historical global cholera pandemics of the nineteenth and twentieth centuries.

Clinical Manifestations

- Acute gastroenteritis: Vomiting is the primary symptom; diarrhea may also be present.
- Noninflammatory diarrhea: Watery diarrhea without high fever or dysentery; low-grade fever possible.
- Inflammatory diarrhea: Grossly bloody diarrhea with mucus and pus; often high fever.
- Persistent diarrhea: Diarrhea lasting more than 14 days.
- Neurologic manifestations: Gastroenteritis and/or diarrhea with paresthesias, respiratory depression, weakness, or any other peripheral or central neurologic manifestation.
- Systemic illness: A multisystem disease of the gastrointestinal (GI) tract and other systems, particularly the circulatory, nervous, and renal systems.

Etiologic Agents

Potential Etiologic Agents

- BW: Potential biological warfare agent; and CW: potential chemical warfare agent.
- Acute gastroenteritis: Norwalk-like virus (vom- itoxin), *Staphylococcus aureus* toxin^{bw}, *Bacillus cereus* toxin, all heavy metals (Hg, As).
- Noninflammatory diarrhea: Enterotoxigenic *E. coli* (ETEC), *Vibrio cholerae*, astroviruses, cali- civiruses (genus Norovirus), rotaviruses, adeno- viruses, *Cryptosporidium parvum*, *Cyclospora cayetanensis*.
- Inflammatory dysentery: *Shigella* spp.^{bw}, *Cam- pylobacter* spp., *Salmonella* spp., Enteroinva- sive *E. coli* (EIEC), Enterohemorrhagic *E. coli* (EHEC), *Vibrio parahaemolyticus*, *Entamoeba histolytica*, *Yersinia enterocolitica*.
- Persistent diarrhea: *Cyclospora cayetanensis*, *Cryptosporidium parvum*, *Entamoeba histo- lytica*, *Giardia lamblia*.

- Neurologic manifestations: Botulinum tox- in^{bw}, OP pesticides^{cw}, thallium, scombrototoxin, ciguatoxin, tetrodotoxin, brevitoxin, saxitoxin, domoic acid, mushroom toxins, post-*Campylo- bacter* Guillain-Barré syndrome.
- Systemic illness: *Listeria monocytogenes*, *Bru- cella* spp.^{bw}, *Trichinella spiralis*, *Toxoplasma gondii*, *Vibrio vulnificus*, hepatitis A virus.

Bioterrorism (BW) Agents and Categories of BW Agents

- *Bacillus anthracis* (BW-A list)
- Botulinum toxin (BW-A list)
- *Brucella* species (BW-B list, Greece-WWII)
- *Shigella* species (BW-B list, N. Africa — World War II, Oregon salad bar)
- *Staph aureus* toxin (BW-B list)

Top Etiologic Agents

- Acute gastroenteritis: Norwalk-like virus > *S. aureus* > *B. cereus*.
- Noninflammatory diarrhea: ETEC (traveler's diarrhea) > *Vibrio cholerae*.
- Inflammatory diarrhea: *Campylobacter* spp. > *Shigella* spp.
- Persistent diarrhea: *Cryptosporidium parvum* > *Cyclospora cayetanensis*.
- Neurologic manifestations: Botulism^{bw}, OP poisoning^{cw}.
- Systemic illness: *Listeria monocytogenes* > *Brucella* spp.^{bw}.

TABLE 12.1 Differential Diagnosis

Acute Onset <6 h = Toxin	Fecal wbc's = Dysentery	Unpasteurized Milk/Cheese	Dysentery + High Fever
<i>Staph aureus</i>	Shigella	Salmonella (eggs)	Salmonella
<i>Bacillus cereus</i>	Salmonella	Campy (chicken)	Shigella
ETEC	Campy	Brucella (goat)	Campy
Ciguatera	EIEC	Listeria (processed meats)	EIEC
Scombroid			
Cholera	Yersinia	TB	Yersinia

Bacterial Diseases

Bacillus anthracis

Microbiology

- Large, spore-forming, Gram-positive bacilli that multiply and align in snakelike chains (“Medusa head”).
- Reservoir: Livestock (cattle > sheep), long-lived spores in soil.
- Endospores: 2–5 microns, environment stable, BW-A list.
- Like *B. cereus*, non-hemolytic on blood agar (culture only in biosafety level 4 [BSL-4] laboratories).

Epidemiology

- Transmission: Direct contact — broken skin > contaminated meat > aerosolized inhaled contact.
- Vehicle: Raw and undercooked meat.
- Inoculum: 6, 60, 6000 spores (secondary to inoculum size and host susceptibility).
- Incubation: 2–60 days.
- Warning: Ranchers, cutaneous > inhalation^{bw} > GI transmission rare.

Clinical Manifestations

- Cutaneous: Black eschar, dramatic local edema, regional lymphadenopathy.
- Gastrointestinal (GI): Nausea and vomiting, malaise, bloody diarrhea, abdominal pain, sepsis, case fatality rate (CFR) 50+%
- Inhalation: Upper respiratory illness (URI) — prodrome, pneumonia, adult respiratory distress syndrome (ARDS), sepsis, hemorrhagic mediastinitis; case fatality rate (CFR) was 70%, now <50% with ICU.

Prevention (Vaccination)

- Primary prevention (vaccination): Inactivated, six-shot series vaccine; cook meat and lamb thoroughly before eating; wear gloves when handling livestock, especially potentially contaminated livestock.
- Secondary prevention (diagnosis): Diagnosis by Gram stain on blood-stool-sputum, C&S (BSL-4), chest x-ray — widened mediastinum.
- Tertiary prevention (treatment): Skin and GI — penicillin; inhalation — doxycycline, quinolones.

***Bacillus cereus* (d-toxin)**

Microbiology

- Large, spore-forming Gram-positive bacilli multiplies and aligns in long chains.
- Reservoir: Like *B. anthracis*, stable spores long-lived in the environment.
- Looks like *B. anthracis* in culture, but hemolytic on blood agar.

Epidemiology

- Transmission: Fecal–oral > direct contact.
- Vehicle: Contaminated meats (subs, Po-boys), gravies, vanilla sauces.
- Inoculum: Low (toxin).
- Incubation: 10–16 hours.
- Warning: French dip, roast beef (Po-boys, subs), sweet sauces and gravies.

Clinical Manifestations

- Acute gastroenteritis: 24–48 hours of nausea, no vomiting, abdominal cramps, watery diarrhea without blood or pus.
- Wound infections: More common with anthrax.
- Subacute bacterial endocarditis: Possible, but rare.

Prevention

- Primary prevention: No vaccine, avoid high-risk foods.
- Secondary prevention: Food and stool culture, diarrheal toxin identification in stool.
- Tertiary prevention: Self-limiting, no antibiotics, supportive care only.

***B. cereus* (enterotoxin)**

Microbiology

- Large, spore-forming Gram-positive bacilli.
- Reservoir: Like anthrax, environmentally stable spores.
- Indistinguishable from *Bacillus cereus* — diarrheal toxin.
- Hemolytic on blood agar, like *B. cereus* (d-toxin).

Epidemiology

- Transmission: Fecal–oral > direct contact.
- Vehicle: Improperly refrigerated cooked and fried meats and especially fried rice.
- Inoculum: Low (toxin).
- Incubation: 1–6 hours.
- Warning: Chinese food, especially spoiled or unrefrigerated meat and fried rice dishes.

Clinical Manifestations

- Acute gastroenteritis: Sudden onset of severe nausea, projectile vomiting, watery diarrhea without blood, pus may rarely be present, self-limiting within 12–48 hours, severe dehydration possible.

Prevention

- Primary prevention: No vaccine, avoid high-risk foods.
- Secondary prevention: Food and stool culture, enterotoxin identification in stool.
- Tertiary prevention: Self-limiting, no antibiotics, supportive care only.

***Brucella* spp.**

Microbiology

- Small, Gram-negative coccobacilli.
- Reservoir: Infected livestock—cattle (*B. abortus*), pigs (*B. suis*), sheep and goats (*B. melitensis*).
- Rose-Bengal test for screening for *B. abortus* antibodies in infected beef cattle and dairy cows.
- Dye inhibition tests to differentiate among *Brucella* spp.

Epidemiology

- Transmission: Fecal–oral > direct contact > aerosol^{bw} (suspect bioterrorism).
- Vehicle: Unpasteurized milk and cheeses, undercooked meats.
- Inoculum: Low.
- Incubation: 7–21 days.
- Warning: Unpasteurized cheeses, especially feta (goat) cheese.

Clinical Manifestations

- Brucellosis: Brucellosis is a systemic illness with high fever, chills, sweats, weakness, myalgias, joint pain, lymphadenopathy, and bloody diarrhea during the acute phase. Chronic illness mimics chronic fatigue syndrome and fibromyalgia.
- Complications: Osteomyelitis, subacute bacterial endocarditis, neuropsychiatric manifestations, especially depression.

Prevention

- Primary prevention: No vaccine; avoid unpasteurized milk and cheeses.
- Secondary prevention: Blood culture and antibiotic sensitivity testing (C&S), serology, Rose-Bengal screening of cattle, *Brucella* blue-ring agglutination tests on raw milk.
- Tertiary prevention: Rifampin and doxycycline every day for 6 weeks. For complications, add an aminoglycoside.

Campylobacter jejuni

Microbiology

- Gram negative, thin, spiral, “gull wing,” motile-darting bacilli, 1 flagellum.
- Reservoir: Wild and domestic birds (especially chickens and turkeys) and mammals.
- United States: No. 2 cause of foodborne bacterial diarrheas, alternating with *Salmonella* spp.
- World: No. 2 cause of traveler’s diarrhea (#1 ETEC).

Epidemiology

- Transmission: Fecal–oral.
- Vehicle: No. 1 undercooked poultry (chicken > turkey) > No. 2 unpasteurized milk > No. 3 contaminated water.
- Inoculum: 10^4 – 10^6 organisms.
- Incubation: 1–5 days.
- Warning: Common, mimics Crohn’s Disease vs. chronic ulcerative colitis (CUC); serious complications = post-infection Guillain-Barré syndrome and arthritis.

Clinical Manifestations

- Prodrome: Fever, headache, nausea and vomiting, malaise, myalgias.
- Colitis: Cramps, 1–10 days diarrhea, mucus, blood (50%), pus (75%), chronic relapsing colitis (differential diagnosis (DDx) includes: Crohn’s and CUC).
- Complications: Guillain-Barré syndrome (10–20%), reactive arthritis (1–14%).

Prevention

- Primary prevention: No vaccine; avoid undercooked poultry and raw, unpasteurized milk.
- Secondary prevention: Fecal polymorphonuclear cells (pmns), Gram stain, C&S, stool for radioimmunoassay detected antigens.
- Tertiary prevention: Macrolides are best (erythromycin, azithromycin) > quinolones > tetracycline (TCN); resistant to penicillin (pcn), vancomycin, trimethoprim-sulfamethoxazole (TMP/SMX).

Raw, Grocery-Bought Chickens

- *Campylobacter*: Currently the most common cause of U.S. foodborne illnesses; found in 42% of grocery chickens; 90% of cultures demonstrated multiple antibiotic resistances.
- *Salmonella*: Found in 12% of grocery chickens; 34% antibiotic resistant.
- *Campylobacter* and *Salmonella*: Found in 5% of grocery-bought chickens.
- Antibiotic resistance: Due to an increase in the use of prophylactic antibiotics in domestic chicken and turkeys (quinolones > tetracyclines > penicillins).

Clostridium botulinum

Microbiology

- Anaerobic, spore-forming Gram-positive bacilli.
- Reservoir: Ubiquitous environmentally stable spores.
- Hemolytic on blood agar.

Epidemiology

- Transmission: Environment > fecal–oral > aerosol^{bw} (suspect bioterrorism).
- Vehicle: Contaminated home-canned fruits, vegetables (garlic), fish; herb-infused salad oils; honey.
- Lethal dose: 1 pg/kg.
- Incubation: Adults, 12–72 hours; infants, 3–30 days.
- Warning: Home-canning, home-preserving, dented tuna and whitefish cans; raw, decomposing marine mammal meat — whale (“muktuk”), seal, walrus.

Clinical Manifestations

- Adult botulism: Nausea and vomiting, diarrhea, then blurred vision, diplopia, dysphagia, descending paralysis, respiratory failure, CFR 50+%, pathognomonic manifestations = descending paralysis and normal mental status.
- Infant botulism: <12 months, lethargic — weak, poor feeding, poor gag and suck, hypotonia = floppy baby/floppy head.
- Warning: Honey in bottled milk.

Prevention

- Primary prevention: Avoid high-risk foods.
- Secondary prevention: Food and stool cultures, identification of botulinum toxin in food, vomitus, and stool.
- Tertiary prevention: Trivalent botulinum antitoxin (adults), botulinum immune globulin and pentavalent antitoxin (infants), life support; broad-spectrum antibiotics to decrease toxin production in gut is controversial.

Clostridium perfringens

Microbiology

- Anaerobic, spore-forming Gram-positive bacilli.
- Reservoir: Domestic livestock and poultry, environmentally stable spores.
- Unique double zone of hemolysis on blood agar.

Epidemiology

- Transmission: Fecal–oral.
- Vehicle: Contaminated poultry, meats, gravies, dried and precooked foods.
- Inoculum: Low (toxin).
- Incubation: 8–16 hours.
- Warning: Dried meats, beef “jerky,” chitterlings (“chitlins”), unrefrigerated meat gravies.

Clinical Manifestations

- Acute gastroenteritis: 24–48 hours of watery diarrhea without blood or pus, nausea, no vomiting, fever rare.
- Wound infections: Gas gangrene potential.
- Enteritis necroticans: Pseudomembranous enterocolitis and pneumatosis intestinalis (“pig-bel” — Papua New Guinea).

Prevention

- Primary prevention: No vaccine; avoid high-risk foods.

- Secondary prevention: Quantitative stool culture to rule out normal flora, Gram stain on stool and pus, identification of enterotoxin in stool.
- Tertiary prevention: Self-limiting; supportive care only.

Escherichia coli

Microbiology

- Aerobic, flagellated Gram-negative bacilli.
- Reservoir: GI flora of animals > humans.
- Three (3) antigen groups: Somatic (O), capsular (K), flagellar (H) antigens.
- Five (5) clinical groups: Enterotoxigenic *E. coli* (ETEC), enteropathogenic *E. coli* (EPEC), enteroinvasive *E. coli* (EIEC), enterohemorrhagic *E. coli* (EHEC, zoonosis), enteroadhesive *E. coli* (EAEC). Clinical groups may overlap.
- ETEC > EPEC > EAEC as causes of traveler’s diarrhea.

Epidemiology

- Transmission: Fecal–oral, person-to-person.
- Vehicle: Food (ground beef, apple/orange juice) > water.
- Inoculum: 10–100 organisms.
- Incubation: 3–14 days.
- Duration: 5–7 days (unless hemolytic uremic syndrome [HUS] or thrombotic thrombocytopenic purpura [TTP] with EHEC).
- Warning: Water parks, wading pools, day care, petting zoos, undercooked hamburgers, unpasteurized fruit juices.

Clinical Manifestations

- ETEC: Two Shiga-like toxins, 1–7 days watery diarrhea without blood or pus.
- EPEC: Same as ETEC, 3–6 days, diarrhea with blood/pus, high fever.
- EA(I)EC: Rare, O124:B17, 3–7 days of low fever, cramps, diarrhea with blood/pus.
- EHEC: O157:H7, 3–10 days of low fever, cramps, diarrhea with blood/pus, HUS 5–10% primarily in children, TTP 5% primarily in adults.

Prevention

- Primary prevention: No vaccine; “boil it, cook it, peel it, or forget it,” bottled drinks, prophylactic antibiotics, Pepto-Bismol®.
- Secondary prevention: Fecal pmns, Gram stain, C&S, ELISAs for ETEC and EHEC.
- Tertiary prevention: Quinolones, resistant to doxycycline and TMP/SMX, avoid anti-motility agents.

Listeria monocytogenes

Microbiology

- Small, aerobic Gram-positive bacilli, non-spore-forming.
- Reservoir: Humans, livestock (cattle), environment.
- Pale colonies on blood agar.

Epidemiology

- Transmission: Fecal–oral > direct contact.
- Vehicle: Unpasteurized milk and soft cheeses, ready-to-eat deli/luncheon meats, hot dogs, sausages.
- Inoculum: Low.
- Incubation: GI, 8–28 hours; systemic listeriosis, 2–6 weeks.
- Warning: Hot dogs and “cold cuts” (processed meats).

Clinical Manifestations

- Acute gastroenteritis: Fever, myalgias, nausea, no vomiting, diarrhea.
- Perinatal listeriosis: Spontaneous abortion (SAB), preterm delivery, stillbirth, puerperal fever — chorioamnionitis and maternal sepsis, neonatal sepsis.
- Geriatric listeriosis: Meningitis, sepsis.

Prevention

- Primary prevention: No vaccine, avoid high-risk foods.

- Secondary prevention: Blood and CSF C&S, serology-Listerolysin O antibodies.
- Tertiary prevention: GI, supportive; systemic-IV penicillin or ampicillin > TMP/SMX.

Salmonella spp.

Microbiology

- Flagellated, Gram-negative bacilli.
- Reservoir: Humans (typhoidal), birds/reptiles (commensal non-typhoidal strains).
- Three (3) antigens: Somatic (O), flagellar (H), and capsular (Vi).
- Environmentally stable — fresh water/sewage.
- Non-typhoidal (*S. choleraesuis*) vs. typhoid — *S. typhi* and *paratyphi* — strains.
- CFR: *S. typhi* > *S. paratyphi* > non-typhoidal *Salmonella* spp.

Epidemiology

- Transmission: Typhoidal — fecal–oral; non-typhoidal — direct contact.
- Vehicle: Contaminated food/water, raw eggs, poultry, reptiles/amphibians (turtles/lizards [iguanas]).
- Inoculum: 10^5 – 10^7 organisms.
- Incubation: Non-typhoidal, 12–48 hours; typhoidal, 7–21 days.
- Warning: Chronic female carriers >40+-year-old females with cholelithiasis = “Typhoid Mary.”

Clinical Manifestations

- Non-typhoidal: 3–10 days of diarrhea with blood and pus, fever, cramps, chronic biliary carriage possible.
- Typhoidal: 5-day prodrome, fever, chills, sore throat, joint pain, rose spots (30%); cramps, hepatosplenomegaly (H/S) (50%), neuropsychiatric symptoms, lymphadenopathy, constipation, no diarrhea, bradycardia, CFR ≤ 30%.
- Complications: Bowel perforations from perforated Peyer’s patch, osteomyelitis.
- Warning: Infants and elderly in homes with pet amphibians and reptiles; turtles > lizards (iguanas) > snakes.

Prevention

- Primary prevention: Three typhoidal vaccines: (1) oral live vaccine, (2) IM, vaccines = approximately 70% efficacy; “boil-it, bottle-it, peel-it, or forget-it”; no amphibian/reptile pets (especially with children and elderly in household).
- Secondary prevention: Blood (50%)/urine/rose spot (70%)/bone marrow (90%) C&S; Widal H/O antibodies.
- Tertiary prevention: Non-typhoidal — quinolones, TMP/SMX; typhoidal — quinolones > ampicillin.

Shigella sonnei

Microbiology

- Aerobic Gram-negative bacilli.
- Reservoir: Humans only.
- Environmentally stable and GI acid-resistant.
- Four (4) serotypes: A — *Shigella dysenteriae*, B — *S. flexneri*, C — *S. boydii*, D — *S. sonnei*.
- World: *S. dysenteriae* most pathogenic.
- United States: *S. sonnei* > *S. flexneri*.

Epidemiology

- Transmission: Fecal–oral, food > water.
- Vehicle: Food, water, anal–oral sex, flies = mechanical vectors.
- Inoculum: 10–100 organisms.
- Incubation: 6–72 hours.
- Warning: Salad bars^{bw}, day care, mental institutions, wading pools, male homosexuals — men having sexual intercourse with men (MSM).

Clinical Manifestations

- *S. sonnei*, *flexneri*, *boydii*: Fever, cramps, watery-then-bloody, mucoid diarrhea with pus; seizures (children).
- *S. flexneri*: Reiter’s syndrome possible in HLA-B27 genotypes.
- *S. dysenteriae*: Shiga toxin, severe dysentery, tenesmus, rectal prolapse, hemolytic uremic syndrome (HUS) in children, thrombotic thrombocytopenic purpura (TTP) in adults.

Prevention

- Primary prevention: No vaccine; handwashing, hygienic food preparation, avoid contaminated drinking water and recreational water.
- Secondary prevention: Fecal pmns, fecal Gram stain, stool C&S, Shiga toxin ELISA, flexible sigmoidoscopy with colon biopsy.
- Tertiary prevention: Quinolones preferred; resistant to ampicillin, TMP/SMX, and TCN.

Staphylococcus aureus

Microbiology

- Aerobic Gram-positive cocci in chains.
- Reservoir: Ubiquitous, man, animals, environment.
- Yellow-gold colonies on blood agar.
- Catalase and coagulase positive.

Epidemiology

- Transmission: Direct > food > fecal–oral > aerosol^{bw} (suspect bioterrorism).
- Vehicle: Contaminated egg/ potato/chicken/seafood salads with mayonnaise > cream pastries > meats.
- Inoculation: Low (toxin).
- Incubation: 1–6 hours.
- Warning: Cream-filled pastries: éclairs, cream puffs, and *doberge* cakes > salads.

Clinical Manifestations

- Acute gastroenteritis: Sudden onset nausea, projectile vomiting, low-grade fever, diarrhea may be present, lasts 24–48 hours.
- Skin infections: Boils, abscesses, impetigo.
- Complications: Osteomyelitis, sepsis.

Prevention

- Primary prevention: No vaccine; avoid high-risk foods, personal hygiene.
- Secondary prevention: Identification of Staph enterotoxins in food, vomitus, and stool.
- Tertiary prevention: Self-limiting, supportive care only.

Vibrio cholerae

Microbiology

- Aerobic, Gram-negative, flagellated, “comma” bacilli.
- Reservoir: Humans.
- Chlorine-resistant, acid-sensitive, thrives in brackish estuaries.
- O1 and O139 strains — cholera toxin blocks Cl pump; O1 strains = classical cholera, *El Tor* strain = current epidemic strain.
- Non-O strains: Mild diarrhea, wound infections.

Epidemiology

- Transmission: Fecal–oral, especially during warm periods.
- Vehicle: Contaminated water > shellfish > non-acidic fish.
- Inoculum: 10^5 – 10^8 organisms.
- Incubation: 1–5 days.
- Warning: Raw/under-boiled shellfish, low gastric pH (B_{12} deficiency, pernicious anemia), blood type O, safest consumption during “R” months (September–April) = folklore, hemosiderosis or iron therapy (*Vibrio* organisms seek iron sources).

Clinical Manifestations

- Classical and *El Tor* strain (90%): Early nausea and vomiting, no fever, painless watery diarrhea, without blood or pus, dehydration, cholera — excretors for days.
- Cholera gravis (10%): Abdominal cramps, fulminant rice — watery diarrhea, metabolic acidosis, hypovolemic shock, cholera — excretors for weeks; CFR 40%.

Non-cholera *Vibrios*

Vibrio parahaemolyticus

- Marine, non-cholera *Vibrio*.
- Salt-tolerant, acid-sensitive (use Tabasco® to prevent infection = folklore).

- Transmission: Raw shellfish (especially raw oysters) > water.
- Clinical manifestations: 1 week fever, nausea and vomiting, watery diarrhea without blood or pus.
- Warning: Avoid raw/undercooked shellfish, especially in warm months, do not count on cold months with “Rs” and Tabasco® to prevent *Vibrio* infections.

Vibrio vulnificus

- Marine, non-cholera *Vibrios*, salt- and acid-resistant.
- Transmission: Raw shellfish-oysters, direct inoculums — seawater.
- Clinical manifestations: Ulcerating cellulitis, *ecthyma gangrenosa*, sepsis has high CFRs.
- Prevention: No raw shellfish; treat all penetrating injuries in seawater with quinolones.
- Warning: Alcoholism, liver disease, especially hemochromatosis.

Prevention

- Primary prevention: Vaccine <50% effective, adequate sewage treatment, breast-feeding protects infants with maternal IgA, avoid raw and undercooked shellfish.
- Secondary prevention: Dark-field microscopy, stool C&S will show blue-green colonies on TCBS agar, rapid stool cholera screens.
- Tertiary prevention: Oral rehydration solutions (ORS), antibiotics may decrease diarrhea and *Vibrio* shedding — doxycycline 300 or ciprofloxacin 1 gm orally every day.

Yersinia enterocolitica

Microbiology

- Gram-negative “safety pin” bacilli, resembling other *Yersinia* spp.
- Reservoir: Humans and many domestic animals, especially pigs.
- Acid and cold stable (Canada, North Europe > United States), heat sensitive.
- Three species: *Y. enterocolitica*, *Y. pseudotuberculosis* (rare in United States), *Y. pestis* plague

(four-corner area of United States = Colorado, Utah, Arizona, and New Mexico).

- Requires special media for C/S (CIN).

Epidemiology

- Transmission: Fecal–oral, food > drinking water > recreational water > blood > nosocomial (households).
- Vehicle: Contaminated pork, tofu, milk, well water.
- Inoculum: High, 10^9 organisms.
- Incubation: 1–3 days.
- Warning: Raw, undercooked pork and pork products (chitterlings = fried pork small intestines), tofu; mimics acute appendicitis, especially during winter (Canada and Northern Europe).

Clinical Manifestations

- Enterocolitis: Canada, Northern Europe, Russia > rare in United States; fever, cramps, diarrhea.
- Acute mesenteric lymphadenitis: Mimics acute appendicitis in adolescents.
- Complications: Erythema nodosum (30%): 2:1 female:male; polyarthrititis (<30%), especially HLA-B27 genotypes; purulent pharyngitis (<10%).

Prevention

- Primary prevention: No vaccine; cook pork well, especially frozen pork; deep-freeze pork < 4°C.
- Secondary prevention: Stool and blood C&S with special media, HAI and ELISA rarely available.
- Tertiary prevention: Susceptible to most antibiotics; quinolones > macrolides.

Viral Diseases

Hepatitis A Virus (HAV)

Microbiology

- Small, ssRNA picornavirus, like polio.
- Reservoir: Humans only.
- Environmentally stable: Heat (to 60°C) and acid (to pH 1.0)-resistant.
- Replicates in duodenal epithelial cells and spreads hematogenously to hepatocytes.

Epidemiology

- Transmission: Fecal–oral, direct person–person > food (shellfish–oysters) > water.
- Vehicle: Human sewage-contaminated water and food, especially berries and greens (lettuce, spring mix, green onions).
- Inoculum: 10^4 – 10^8 virions.
- Incubation: 2–6 weeks.
- Warning: Day care/mental facilities, male homosexuals; occupational exposures — sewer workers, primate handlers.

Clinical Manifestations

- Prodrome: Anorexia, fever, nausea and vomiting, malaise, lethargy.
- Hepatitis: Right upper quadrant (RUQ) pain, hepatomegaly, dark urine, pale feces, jaundice for up to 6 weeks (adults 66%), infants/toddlers often asymptomatic (80%); lifelong immunity, CFR 0.5%.

Prevention

- Primary prevention: Two formalin-inactivated vaccines, two (2) doses, 90% efficacy.
- Secondary prevention: IgM RIA or ELISA, IEM, PCR for RNA amplification.
- Tertiary prevention: Supportive therapy.

Hepatitis E Virus (HEV)

Microbiology

- Small, round ssRNA calicivirus.
- Reservoir: Humans only.
- Environmentally stable: Acid, salt, cold-resistant; probably chlorine-sensitive.
- Never successfully cultured *in vitro*.

Epidemiology

- Transmission: Fecal–oral, water > food (especially shellfish).
- Vehicle: Human waste-contaminated drinking water.
- Inoculum: High.
- Incubation: 2–8 weeks.
- Warning: Pregnant women traveling in developing countries (high CFR).

Clinical Manifestations

- Hepatitis: Occurs predominantly in developing areas in 15- to 40-year-olds, especially pregnant women; high bilirubin levels, deeper jaundice than HAV, otherwise same as HAV; no chronic carriers. CFR 0.5–3%; CFR in pregnancy 10–20% (mechanism unknown).

Prevention

- Primary prevention: No vaccine; use boiled or bottled drinking water in developing countries.
- Secondary prevention: Immunofluorescent electron microscope (IFEM), viral RNA amplification by PCR; ELISA and Western blot for antibodies not widely available.
- Tertiary prevention: Supportive therapy only.

Norwalk-like Viruses

Microbiology

- Small, round caliciviruses (virions resemble six-pointed stars) and astroviruses (virions resemble snowflakes).
- Reservoir: Humans and shellfish.
- Linear, ssRNA genome.
- Intracellular replication within jejunal villi.
- Heat (to 60°C), acid (to pH 3.0), and chlorine-resistant.

Epidemiology

- Transmission: Fecal–oral, shellfish > salad > person to person > water.
- Vehicle: Human sewage-contaminated shellfish.
- Inoculum: Low, < 10² virions.
- Incubation: Short, 24–48 hours.
- Warning: Raw/inadequately cooked shellfish, seafood salads, food handlers, travel cruises, naval vessels, sea cruises.

Clinical Manifestations

- Acute gastroenteritis: 12–60 hours of watery diarrhea (80%) with no mucus, blood, or pus; abdominal cramps (80%), nausea and vomiting (50%), fever (50%), headache (50%), and myalgias (< 50%).
- Always self-limited.

Prevention

- Primary prevention: No vaccine; well-cooked shellfish; proper human waste disposal on shellfish harvesting (especially oyster-fishing) boats.
- Secondary prevention: EM, IEM; EIA-RIA-PCR are not widely available.
- Tertiary prevention: Rehydration, supportive therapy.

Rotaviruses

Microbiology

- Virions resemble small round wheels (rotors), two concentric icosohedral shells, surface protein bumps.
- Reservoir: Humans, domestic animals, mammals and birds.
- Environmentally stable: Acid, salt, cold, and chlorine resistant.
- Six (6) serotypes: A–F (A is most common causative agent); infection confers limited immunity.

Epidemiology

- Transmission: Fecal–oral.
- Vehicle: Contaminated water > food > person-to-person.
- Inoculum: 10⁵–10¹⁰ virions.
- Incubation: 1–3 days.
- Warning: Nurseries, day care, diaper-change stations (diaper-changers acquire 10⁶ virions on their surfaces per change).

Clinical Manifestations

- Acute gastroenteritis: Nausea and vomiting precede 4–5 days of watery diarrhea without mucus, blood, or pus; low K⁺/Cl[−]-metabolic alkalosis mixed with hypoperfusion metabolic acidosis possible; most common in infants 6–24 months old. Mimics pyloric stenosis during prodrome.

Prevention

- Primary prevention: RotaShield® live vaccine, 80% efficacy, withdrawn due to infant small bowel intussusception; breast-feeding confers IgA protection.
- Secondary prevention: Stool EM, ELISA, latex particle agglutination; serum ELISA.
- Tertiary prevention: Oral rehydration, supportive treatment, no anti-motility agents.

Protozoal Diseases

Entamoeba histolytica

Microbiology

- Parasitic, not free-living.
- Reservoir: Humans, domestic pets.
- Cysts infective, prefer warm climates, iodine/chlorine resistant; excyst in small intestine to allow trophozoites to invade colorectal mucosa.
- Pathogenic and nonpathogenic strains (*E. dispar*) infect 10% of world population.

Epidemiology

- Transmission: Fecal–oral, person-to-person.
- Vehicle: Contaminated drinking water, fruits/vegetables irrigated with human wastes.
- Inoculum: Low.
- Incubation: 1–14 weeks.
- Warning: Susceptibles include male homosexuals (MSM), infants, pregnant, malnourished.

Clinical Manifestations

- Asymptomatic cyst passers (80%): Usually due to *E. dispar*.
- Amebiasis (10%): Watery diarrhea without blood and pus, fever.
- Amebic dysenteric colitis (10%): Diarrhea with blood, pus and mucus, fever, weight loss, perianal ulcers, perforated megacolon.
- Extraintestinal amebiasis (1%): 3–10% colitis, liver abscess, right > left (rupture into adjacent body cavities).

Prevention

- Primary prevention: No vaccine, no chemoprophylaxis, boil water, adequate sanitation.
- Secondary prevention: Stool trophozoites, flexible sigmoidoscopy with colon biopsy, stool/serum antigen detection (ELISA), stool/serum anti-

bodies (antibody detection, acute-convalescent sera-fluorescent antibodies), liver ultrasound > CT-guided — fluid aspirate.

- Tertiary prevention: Cyst passers/colitis: metronidazole 750 mg three times daily for 10 days; extraintestinal: same and paromomycin 25–35 mg/kg/d in three daily doses for 10 days.

Giardia lamblia

Microbiology

- Flagellated, upper GI (duodenal) protozoan.
- Reservoir: Humans and wild mammals, especially beavers and raccoons.
- Infective stage: Fecal cysts; acid, heat, cold, and chlorine resistant.
- Sexual stage: Trophozoites, detected by Entero-test®, or passed during severe diarrhea.

Epidemiology

- Transmission: Fecal–oral, waterborne > person-to-person > foodborne.
- Vehicle: Cyst-contaminated drinking water, or direct contact.
- Inoculum: Low, few cysts.
- Incubation: 1–2 weeks.
- Warning: Inadequate water treatment in mountain communities, campers in beaver habitats, wading pools, day-care facilities, food handlers, male homosexuals.

Clinical Manifestations

- Cyst passers: No symptoms.
- Acute diarrhea (90%): 1–5 days, and malaise (80%), nausea, cramps/bloating, anorexia (70%), fever and vomiting rare.
- Chronic diarrhea: Greasy foul-smelling stools, high fecal fat (75%), no blood or pus, malabsorption (30%), lactose intolerance (30%), >10-lb. wt loss (65%).

Prevention

- Primary prevention: Proper water treatment, especially filtration; treat all cyst passers.
- Secondary prevention: Fecal cysts and trophozoites, stool antigen detection by ELISA, Enterotest® or duodenal aspirate for trophozoites.
- Tertiary prevention: Metronidazole (250 mg) 3 times daily for 7 days.

Coccidial Protozoan:

Cryptosporidium parvum

Microbiology

- Intracellular coccidian, like malaria.
- Reservoir: Juvenile domestic animals and pets, humans.
- Heat, cold, iodine, and chlorine-resistant; infective sporocysts (4–6 m); asexual and sexual replication cycle in jejunum.
- Sporocysts take acid-fast stain and immunofluoresce.

Epidemiology

- Transmission: Drinking water contaminated with feces of juvenile livestock (especially calves), pets, infected humans.
- Vehicle: Sporocysts.
- Inoculum: Very low, few cysts.
- Incubation: 3–10 days.
- Warning: HIV, male homosexuals, day care, child travelers, petting zoos, occupational exposures — wild animal handlers.

Clinical Manifestations

- Immunocompetent: Low fever, malaise, 3 days to 3 weeks of watery diarrhea without blood or pus.
- Immunocompromised (HIV): Severe, prolonged, voluminous diarrhea, 25 bowel movements/day, 3 L/day, weight loss, malabsorption.
- Complications: Ascending cholangitis, acalculous cholecystitis.

Prevention

- Primary prevention: No vaccine; drinking water filtration <3 microns, bottled drinking water for susceptibles (AIDS).
- Secondary prevention: Fecal acid-fast stain and autofluoresces under ultraviolet light, jejunal biopsy.
- Tertiary prevention: Supportive; consider paromomycin, 750 four times daily for 4 days and somatostatin, 500 mcg four times daily for 4 days to control diarrhea.

Coccidial Protozoan:

Cyclospora cayatenesis

Microbiology

- Coccidian with large, iodine/chlorine-sensitive sporocysts (8–10 m) that require maturation to be infective for man.
- Reservoir: Humans, no animals.
- Asexual/sexual replication in jejunal epithelium.
- Takes acid-fast stain, autofluoresces under ultraviolet light.

Epidemiology

- Transmission: Fecal–oral, food > water, not person-to-person.
- Vehicle: Contaminated foods (raspberries, strawberries, lettuce) or drinking water.
- Inoculum: Low.
- Incubation: 1 week.
- Warning: Travel to South Africa or Nepal, high-risk foods, susceptibles include children, HIV/AIDS patients.

Clinical Manifestations

- Immunocompetent: 5 days of watery diarrhea without blood or pus; anorexia, cramps, nausea without vomiting, no weight loss.
- Immunocompromised: More severe, prolonged diarrhea with weight loss.

Prevention

- Primary prevention: No vaccine; filtered, bottled, or chlorine/iodine treated drinking water for susceptibles and in Nepal; avoid unwashed South African berries such as raspberries, strawberries, blueberries.
- Secondary prevention: Fecal acid-fast, UV-fluorescent microscopy, jejunal biopsy.
- Tertiary prevention: TMP/SMX ds, twice daily for 7 days; 14–30 days in immunocompromised susceptibles.

Coccidial Protozoan:

Isospora belli

Microbiology

- Coccidian protozoan with infective, football-shaped sporocysts.
- Reservoirs: Humans, no animals.
- Sporocysts excyst in jejunum and invade epithelium for asexual and sexual replication.
- Cysts take acid-fast stains and autofluoresce under UV light microscopy.

Epidemiology

- Transmission: Fecal–oral, drinking water > food; person-to-person transmission unlikely.
- Vehicle: Human feces-contaminated water, food.
- Inoculum: Low.
- Incubation: 1 week.
- Warning: Travel to tropical, developing areas, especially by immunocompromised susceptibles (AIDS).

Clinical Manifestations

- Immunocompetent: 2–3 weeks of watery diarrhea without blood or pus; mimics ETEC and EPEC — traveler's diarrhea.
- Immunocompromised: Prolonged (6 months) watery diarrhea, abdominal cramps and pain, nausea without vomiting, weight loss.

Prevention

- Primary prevention: No vaccine; adequate water and sewage treatment; avoid human waste-fertilized or irrigated fruits and vegetables.
- Secondary prevention: Acid-fast, UV-fluorescing football-shaped cysts in stool.
- Tertiary prevention: TMP/SMX doses 2 times daily for 10 days.

Coccidial Protozoan:

Toxoplasma gondii

Microbiology

- Coccidian parasite.
- Reservoir: Rodents and wild cats > domestic cats > sheep > pigs > deer.
- Oocysts excreted in cat feces, mature and become infective.
- Two trophozoite forms: Tachyzoites (replicative) and bradyzoites (encysting).

Epidemiology

- Transmission: Fecal–oral > food (pork, lamb, venison).
- Vehicle: Cat feces; raw and undercooked pork, lamb, venison.
- Inoculum: High.
- Incubation: 6–10 days.
- Warning: Pregnancy, *outside* cat litter boxes, wild (feral) cats.

Clinical Manifestations

- Asymptomatic: 50+%.
- Immunocompetent: 2%, URI-like, low fever, cervical lymphadenopathy.
- Immunocompromised: Encephalomyelitis, myocarditis, pneumonia.
- Congenital: Slow onset mental retardation, cerebral palsy, seizures, intracranial calcifications, chorioretinitis, microcephaly.

Prevention

- Primary prevention: No vaccine; avoid high-risk foods and practices.
- Secondary prevention: Parasites in blood, CSF, lymph, sputum, placenta, cord, amniotic fluid; IgM > IgA antibodies, PCR on white blood cells and CSF.
- Tertiary prevention: Asymptomatic — no treatment; others — spiramycin or pyrimethamine and sulfadiazine.

Parasitic Diseases

Trichinella spiralis

Microbiology

- Nematodes with characteristic sexual organs (stichosomes) on posterior ends.
- Reservoir: Encysted larvae in muscles of domestic (pigs) and wild (bear, moose) animals.
- Sexual mating in small intestine produces larvae that encyst in muscles, especially cranial nerve (CN)–subserved muscles (particularly extraocular muscles) and diaphragm.

Epidemiology

- Transmission: Foodborne, pork > wild game.
- Vehicle: Raw and undercooked pork > moose and bear.
- Inoculum: Low, few cysts.
- Incubation: 2 days to 8 weeks.
- Warning: Pork sausage, *boudin*.

Clinical Manifestations

- Trichinosis: Months of nausea, vomiting, diarrhea without blood or mucus, then high fever, periorbital edema, myalgias, muscle masses, CN palsies.

Prevention

- Primary prevention: No vaccine; avoid raw and undercooked high-risk meats, especially pork.
- Secondary prevention: Eosinophilia, encysted larvae in muscle biopsies, serology, rarely adult worms in stool.
- Tertiary prevention: Supportive, mebendazole.

Cruise Ship Diarrhea

- Bon Voyage

TABLE 12.2 Diarrhea Outbreaks (31): 1986–1993

Agents	No. Outbreaks (%)	People Sick
Bacteria	12 (39)	2150
ETEC	5	1155
Shigella	4	450
Salmonella	2	380
<i>Staph aureus</i>	1	165
Norwalk/NLV	9 (29)	3028
Unknown	10 (32)	3049
Total	31 (100)	10,377

TABLE 12.3 Diarrhea Outbreaks (5): 2002

Lines and Ships	People Sick	People Aboard
Carnival <i>Fascination</i>	203	3348
Carnival <i>Conquest</i> (#1)	230	4320
Disney <i>Magic</i>	160	3488
Holland Am. <i>Amsterdam</i>	181	1878
Radisson 7- <i>Seas Mariner</i>	21	1035
Totals (Source: CDC-VSP)	795 (Incid. rate = 5.99%)	14,069 (Attack rate = 5.65%)

TABLE 12.4 Diarrhea Outbreaks (4): 2003

Lines and Ships	People Sick	People Aboard
Sun Princess	296	2906
Sun Cruises Sundream	107	1488
Royal Olympic Olympia Voyager	40	1112
Carnival Spirit	112	3045
Totals (Source: VSP to 3/1/03)	555 (Incid rate = 6.94%)	8551 (Attack rate = 6.49%)

TABLE 12.5 Food Items (31 Outbreaks): 1986–1993

Food Items Implicated	No. Outbreaks/Agent id.	Organisms
Scallops (undercooked)	3	ETEC
Eggs (unpasteurized)	2	Salmonella
Potato salad (onshore)	2	<i>Shigella</i> spp.
Fresh sliced fruits	1	Norovirus-NLV
Calamari (marinated)	1	Unknown
Chicken or lobster salad	1	Norovirus-NLV
Smoked fish salad	1	Unknown
Flan (Sp., custard)	1	<i>Staph aureus</i>
Ice cream	1	Norwalk virus

Prevention and Control

- Wash hands frequently with soap and water.
- Cook all seafood thoroughly.
- Drink bottled water.
- Serve pasteurized eggs.
- Prevent food handlers from working while ill.
- Avoid onshore caterers for offship excursions.
- Avoid salads and all raw fruits that you do not peel.
- Report outbreaks promptly to the Vessel Sanitation Program (VSP) of the CDC.

Conclusions

Final Recommendations

- Wash hands frequently after using restroom, shaking hands, and before eating.
- Eat only pasteurized dairy products and eggs.
- Avoid tapwater and ice if uncertain about quality.
- Recognize high-risk foods: creams, custards, eggs, berries, lettuce (salads), undercooked fish and shellfish.
- When traveling “Boil it, bottle it, peel it, or forget it.”

Seafood Poisoning

Chapter Outline

History

- Ancient history
- Modern history

Epidemiology

- Burden of disease
- Determinants of seafood-borne disease

Definitions

- Plankton
- Marine toxins
- Feeding habitats and feeding habits

Shellfish poisoning

- Paralytic shellfish poisoning
- Neurotoxic shellfish poisoning
- Diarrhetic shellfish poisoning
- Amnesic shellfish poisoning

Pfiesteria-complex organisms (PCOs)

Crustacean poisoning

Finfish poisoning

- Ciguatera fish poisoning
- Scombroid fish poisoning
- Tetrodotoxic fish poisoning
- Miscellaneous saltwater fish poisoning
- Freshwater fish poisoning
- Marine botulism

General management strategies

Prevention strategies

Conclusions

History

Ancient History

- Ancient Israel: Mosaic law forbade consumption of all fish without scales (Example: all pufferfish [most are tetrodotoxic] and eels [many are ciguatoxic]).
- Old Testament: The Red Sea, normally bright blue, was probably so named after a red tide harmful algal bloom (HAB).
- Old Testament: Moses probably “parted” the Red Sea in a known tidal zone, where shellfish and crustaceans were routinely harvested between tides.

Modern History

- London, 1774: William Anderson, M.D., Royal Navy, ship’s surgeon, described an outbreak of ciguatera poisoning on Capt. James Cook’s second voyage to the South Pacific after the crew consumed a red snapper caught in the New Hebrides.
- Berlin, 1885: Rudolph Virchow, M.D., performed forensic autopsies on the 6 of the 26 severely poisoned patients who died after consuming toxic blue mussels in a Berlin restaurant.
- Maryland, 1997: Massive *Pfiesteria*-associated dinoflagellate fish kills (sea bass, speckled trout, and mullet) reported in Chesapeake Bay.

Epidemiology

Burden of Disease

- Most shellfish and 300+ finfish species: Can cause poisonings with potentially lethal (case fatality rate [CFR] 1–62%) toxins not inactivated by cooking, freezing, smoking, or salting.
- 70% of the world's population: Lives near seacoasts; seafood provides 40% of world's protein.
- 25,000–50,000 cases of ciguatera occur annually: 2300 cases/year in the United States and Canada, and 5 cases/10,000 in Florida.
- Scombroid fish poisoning: Causes 5% of all CDC-reported foodborne diseases and 37% of all reported seafood-borne disease.

Determinants of Seafood-Borne Disease

- More frequent harmful algal blooms (HABs): HABs are a result of global warming; irrigation and wastewater runoff = agricultural runoff (nitrogen-loading) + sewage runoff (sulfur-loading) + household detergent runoff (phosphorous-loading) + soil sediment (pesticides); more natural disasters = hurricanes/typhoons, earthquakes; and increased trade and industrialization = port docks/seawalls; ship ballast/sewage.
- Coral reef destruction: Filtering reefs are often damaged or destroyed by atmospheric and deep-sea nuclear warhead testing; drag-net fishing methods; and the pacific crown-of-thorns starfish, *Acanthaster planci* (see Figure 13.2).
- Long-line commercial fishing: High levels of scombrottoxins are produced in deep sea finfish (tuna, cobia, mahi mahi, wahoo) hooked and dying in warm water over 20+ hours.

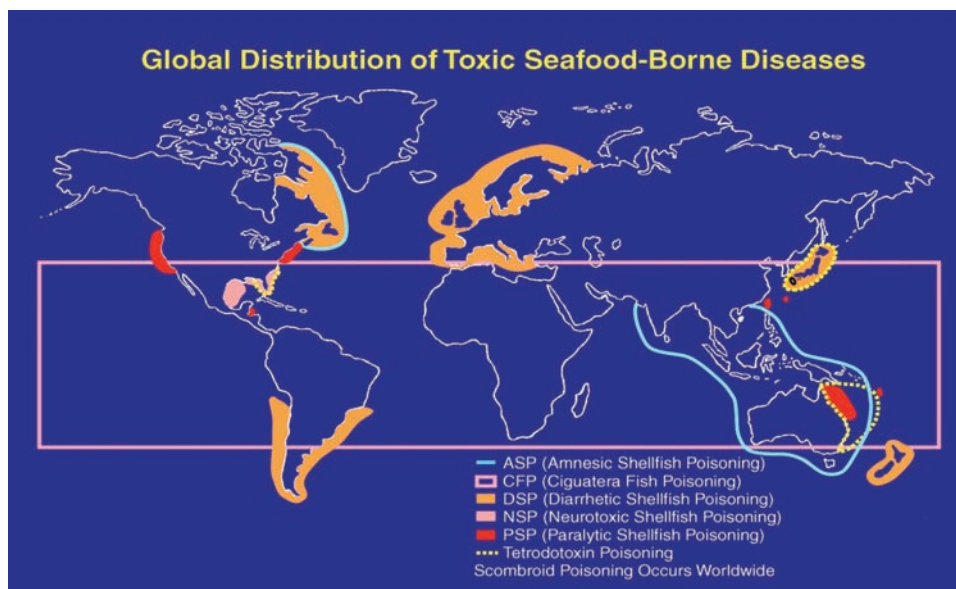


Figure 13.1 A world map depicting the global ranges of the most common types of toxic seafood poisonings.

Definitions

- Plankton: Phytoplankton vs. zooplankton
- Marine toxins: Exotoxins vs. endotoxins
- Marine habitats: Reef vs. deep sea
- Feeding habits: Filtering vs. reef-grazing

Plankton

Phytoplankton

- Chlorophyta: Green algae.
- Chrysophyta: Yellow-brown algae and diatoms.
- Cyanophyta: Freshwater blue-green algae (see Figure 13.4).
- Euglenophyta: Freshwater euglenoids — non-toxic pond dwellers.
- Pyrrophyta: Red tide dinoflagellates — largest number of toxic plankton species (10%), includes *Pfiesteria piscicida* (see Figure 13.5).

Zooplankton

- Larval crustaceans: Xanthid (Xanthidae) crabs — bioaccumulate palytoxin.
- Larval coelenterates: Zoanthid corals — primary palytoxin producers in reef habitats (see Figure 13.6).
- Larval marine round and flatworms: Tetrodotoxin (TTX) producers.
- Larval copepods, krill and shrimp: Nontoxic; preferred food source by marine mammals, especially whales.

Marine Toxins

Bioaccumulated Exotoxins: Primary Sources

- Saxitoxin: *Alexandrium* species dinoflagellates.
- Gonyautoxins: *Alexandrium* species dinoflagellates.
- Brevetoxins: *Gymnodinium breve* dinoflagellates.

- Okadaic acid: *Dinophysis* species dinoflagellates.
- Domoic acid: *Pseudonitzschia pungens* diatoms.
- Palytoxin: Zoanthid coral-feeding parrotfish (rarely triggerfish) and all tidal xanthid crabs.
- Ciguatoxins: *Gambierdiscus toxicus*.
- Shark carchatoxins: Bull and tiger sharks; primary source of bioaccumulated exotoxin is unknown.
- Buffalo fish myotoxin: Primary source of bioaccumulated freshwater exotoxin unknown.

Endogenous Endotoxins: Primary Sources

- Scombrotoxins: Produced by gut bacteria-catalyzed L-histidine decarboxylation to histamine and its primary metabolite, saurine, in decomposing deep-sea finfish, especially scombroid species (tuna, mackerel, albacore, skipjack, and bonito), and even non-scombroid species (mahi mahi, wahoo, cobia, and amberjack).
- Tetrodotoxin: Produced by endosymbiotic bacteria in all pufferfish (porcupine fish, globefish, balloon fish, blowfish, toadfish), marine sunfish, and many other marine animals (stored in fish skin, gonads, liver, roe) and invertebrates (blue-ringed octopus — saliva), and amphibians (newts and toads — skin secretions).

Feeding Habitats and Feeding Habits

Reef: Filter Feeders

- Bivalved mollusks: Clams (*Saxidomus* species), cockles, blue mussels (*Mytilus* species), oysters, and scallops can all bioaccumulate and concentrate both dinoflagellate and diatom exotoxins.
- Coelenterates: Some anemones and all zoanthid corals produce palytoxin (parrotfish and, occasionally, triggerfish feed on these and bioaccumulate palytoxin).

TABLE 13.1 Biotoxin Potency

Biotoxins: in Potency Order	LD₅₀ (mcg/kg IV in mice)
#1 = Botulinum toxin (marine mammals)	0.0026
#2 = Palytoxin (parrotfish)	0.15
#3 = Frog batrachotoxin	2.0
#4 = Taipan (snake) venom	2.0
#5 = Tetrodotoxin (puffers)	9.0
#5 = Saxitoxin (shellfish)	9.0
#6 = Tiger snake venom	25.0
#7 = Cobra (snake) venom	75.0

Deep-Sea/Reef: Baitfish Feeders

- Predatory deep-sea finfish: Mackerel and tuna (Scombridae), and non-scombroid amberjack, bonito, cobia, wahoo, and mahi mahi can produce endogenous scombrototoxins on slow, high-temperature decomposition of muscle protein (histidine).
- Predatory reef fish: All can bioaccumulate ciguatoxins.
 - Carnivorous: Barracuda > grouper, jacks, and all snappers (especially red snappers). Miscellaneous potentially ciguatoxic reef-dwelling fish: amberjack, sea bass.
 - Herbivorous: Triggerfish > surgeonfish and parrotfish (palytoxic).

Shellfish Poisoning

Paralytic Shellfish Poisoning

- Agents: Alexandrium species dinoflagellates, *Gymnodinium catenatum*, *Pyrodinium bahamense*.
- Toxins: Saxitoxin, neosaxitoxin, gonyautoxins #1–#8, epigonyautoxin.
- LD₅₀ (IV in mice): 9 mcg/kg.
- Mechanism: Reversible binding to the outer pore of the sodium (Na) channel, blocking Na influx, preventing depolarization and nerve action potential (NAP) propagation.
- Vectors: Mussels and clams > oysters, scallops, and Southern pufferfish (most puffers are tetrodotoxic; Gulf Stream puffers may also be saxitoxic).
- Incubation: 30 minutes to 2 hours.
- Symptoms: Perioral burning and tingling, then paresthesias that spread from lips, to tongue, to throat; generalized weakness and numbness; nausea and vomiting; descending paralysis with dysphagia and dysphonia; respiratory failure; cardiovascular instability.
- Diagnosis: Mouse bioassay, thin layer chromatography (TLC), high-pressure liquid chromatography (HPLC), RIA, ELISA.
- Treatment: Protect airway, gastric lavage then AC, IV fluids, mechanical ventilation, vasopressors.
- Prognosis: Symptoms peak in 12–24 hours and resolve in 3–4 days, CFR 8.5–14%; rare complications and/or sequelae with appropriate ICU care.
- Prevention: Close beds when toxin levels exceed 80 mcg/kg; avoid eating all pufferfish; adhere to shellfish consumption advisories.

Neurotoxic Shellfish Poisoning

- Agent: *Gymnodinium* (*Karenia*) *breve*, formerly *Phytodiscus brevis*.
- Toxins: Brevetoxins (polycyclic ethers).
- LD₅₀: Unknown; no human fatalities.
- Mechanism: Forced opening of Na channels with increased Na influx and prolonged depo-

larization (opposite of saxitoxin and tetrodotoxin [TTX]).

- Vectors: Clams > oysters.
- Incubation: 15 minutes to 3 hours.
- Symptoms: Mild ciguatera-like symptoms with perioral paresthesias and temperature reversal; rarely nausea and diarrhea; unique conjunctivitis, rhinitis, and/or asthmatic bronchitis from aerosolized brevetoxins in breaking surf.
- Diagnosis: By history, TLC or HPLC.
- Treatment: Supportive only.
- Prognosis: Full recovery in 48 hours.
- Prevention: Monitor shellfish bed dinoflagellate counts; adhere to shellfish consumption advisories.

Diarrhetic Shellfish Poisoning

- Agents: *Dinophysis acuminata* (Atlantic Ocean) and *Dinophysis fortii* (Pacific Ocean).
- Toxins: Okadaic acid > dinophysotoxins, pectenotoxins, and yessotoxin.
- LD₅₀: Unknown; no human fatalities reported.
- Mechanism: Inhibits protein phosphatases, disrupting cell metabolism; deregulates mitosis promoting neoplasia, specifically benign gastric tumors.
- Vectors: Blue mussels — *Mytilus edulis* (Atlantic) and *Mytilus californianus* (Pacific) > clams (*Saxidomus* spp.) > cockles, oysters, and scallops.
- Incubation: 30 minutes to 15 hours (mean 5–6 hours).
- Symptoms: Exclusively gastrointestinal with nausea, vomiting, cramping abdominal pain, severe diarrhea (>20 stools/day), no CNS symptoms.
- Diagnosis: Mouse bioassay, HPLC.
- Treatment: Supportive, IV fluid and electrolyte replacement.
- Prognosis: Self-limited, symptoms resolve within 3 days; no fatalities.
- Prevention: Monitor shellfish bed dinoflagellate counts; adhere to local shellfish consumption advisories.

Amnesic Shellfish Poisoning

- Agents: The diatom, *Pseudonitzschia* (*Nitzschia*) *pungens*, and, rarely, some red algae (*Chondria* species).
- Toxin: Domoic acid (from the Japanese “*domoi*” for seaweed); used in Japan as a very effective antihelminthic agent.
- LD₅₀: Unknown; 4 deaths reported in elderly patients over the age of 70.
- Mechanism: CNS glutamate receptor stimulation causing Na channel up-regulation and unopposed, prolonged depolarization with increased Na and Ca influx and neuronal cell lysis.
- Vectors: Blue mussels (*Mytilus* species) > razor clams (*Seliqua patula*).
- Incubation: <24 hours.
- Symptoms: Initial nausea, vomiting, diarrhea, and cramping abdominal pain; then ataxia, confusion, dizziness, headache, seizures, potentially chronic antegrade and short-term memory loss, especially in the elderly. Mimics Alzheimer’s disease.
- Diagnosis: Mouse bioassay, HPLC.
- Treatment: Supportive only.
- Prognosis: Full recovery within 48 hours; persistent short-term memory loss possible (mimics Alzheimer’s), especially in the elderly.
- Prevention: Closure of shellfish beds when domoic acid levels exceed 20 mcg/g shellfish; always adhere to local shellfish consumption advisory advisories (particularly in Canada).

Pfiesteria-Complex Organisms (PCOs)

- Agents: *Pfiesteria piscicida* and 10–12 related dinoflagellates, all collectively known as *Pfiesteria*-Complex Organisms (PCOs).
- Toxins: (1) Water-soluble, ichthyotoxic neurotoxin; (2) lipid-soluble necrotoxin causing “punched out” necrotic fish lesions.
- LD₅₀: No human fatalities, but neurotoxin is always lethal in fish.
- Mechanism: Like brevetoxins, aerosolized neurotoxins force open Na channels, prolonging depolarization, especially in brain.
- Vectors: No seafood vectors; does not enter human seafood chain.
- Incubation: 2 weeks after aerosol exposures to PCO toxins.
- Symptoms: Confusion and/or memory loss and more than three (3) of the following symptoms: headache, skin rash, conjunctivitis, upper respiratory tract (URT) irritation and sensitivity, muscle cramps, and any type of gastrointestinal symptoms (abdominal cramps, nausea, vomiting, usually no diarrhea).
- Diagnosis: By history of aerosol exposure only.
- Treatment: Supportive only.
- Prognosis: Symptoms resolve in 1–2 weeks.
- Prevention: Avoid swimming, skiing, fishing, and all other recreational exposures in all waters with extensive fish kills; citizens should immediately report large fish kills to state environmental and public health agencies and to the CDC.

Crustacean Poisoning

- Agents and toxins: Bioaccumulated red algal gonyautoxins and zoanthid coral palytoxin; endogenous tetrodotoxin.
- LD₅₀ (IV in mice): Gonyautoxins and tetrodotoxin (TTX) — 9 mcg/kg; palytoxin — 0.15 mcg/kg.
- Mechanism: Gonyautoxins and TTX reversibly bind to outer pore of Na channels, decreasing Na influx and depolarization; palytoxin inhibits Na-K ATPase, Na and K can enter but cannot leave axon, Ca cannot enter, causing hypocalcemic tetanic contractions.
- Vectors: Most Indo-Pacific xanthid crabs, terrestrial coconut crab, and Asian horseshoe crabs; rarely herbivorous reef triggerfish and parrotfish (palytoxin).
- Incubation: 10–15 minutes to 3–4 hours.
- Symptoms: Palytoxic — initial nausea, vomiting, diarrhea, facial-to-limb paresthesias; tonic-clonic seizures with rhabdomyolysis, myoglobinuria, acute tubular necrosis (ATN); cardiovascular collapse. TTX — respiratory paralysis.
- Diagnosis: Mouse bioassay, TLC, HPLC, high levels of serum creatine phosphokinase (CPK) from rhabdomyolysis.
- Treatment: Protect airway; gastric emptying, orogastric lavage with NaHCO₃, then activated charcoal (AC), 1 g/kg; mechanical ventilation; consider multi-dose AC, alkalinize urine, forced osmotic diuresis with mannitol.
- Prognosis: CFR-TTX: 62%, CFR-palytoxin: >60%; most recover in ICU by 48 hours to 5 days.
- Prevention: Avoid unusual crab species and local crab “miso” — soups made from tidal xanthid crabs; always adhere to local seafood consumption advisories.

Finfish Poisoning

Ciguatera Fish Poisoning

- Agents: Dinoflagellates — *Gambierdiscus toxicus* (worldwide), *Ostreopsis lenticularis* (Caribbean only).
- Toxins: Three neurotoxins = ciguatoxin, gambierol, and scaritoxin; one myotoxin = maitotoxin.
- LD₅₀ (IV in mice): Ciguatoxin — 0.45 mcg/kg; maitotoxin — 0.05 mcg/kg.
- Mechanism: Ciguatoxic-forced opening of Na channels with increased Na influx, prolonged depolarization, and myospastic contractures. Maitotoxic-forced opening of Ca channels with increased Ca influx and prolonged myospasticity.
- Vectors: >100 reef fish species; predatory reef fish — barracuda, grouper, snapper, all jacks, wrasse, moray eel; herbivorous reef fish — filefish, parrotfish, surgeonfish, triggerfish.
- Incubation: Within 24 hours.
- Symptoms: Cramps, nausea, vomiting, diarrhea (75%); metallic oral taste, perioral and distal paresthesias, glove and stocking numbness, palmar pruritus, hot-cold sensation reversal, tremor, ataxia, vertigo, decreased DTRs then seizures, myopathy, arthralgias, weakness, stupor-coma.
- Diagnosis: Mouse bioassay, RIA, stick-enzyme immunoassay (IA) (Cigua-Check®) on suspected seafood, gas chromatography and mass spectrometry (GC/MS).
- Treatment: Supportive; anticonvulsants (benzodiazepines [BZs]); IV mannitol 1 g over 45 minutes two times within 24–48 hours and gabapentin 1200–2400 mg/d orally for chronic symptoms (untested); avoid fish, alcohol, nuts for 3–6 months, which may precipitate recurrent pruritus (mechanism unknown).
- Prognosis: Symptoms resolve in 10–58 hours; persistent distal numbness, pruritus and temperature reversal possible.

- Prevention: Avoid ciguatoxic species, especially barracuda and fish organs (especially liver, ovaries, and roe); adhere to all advisories; promote healthy coral reefs, limit drag-line fishing, ban atmospheric and deep-sea nuclear weapons testing, and support increased crown-of-thorns starfish (*Acanthaster planci*) control.

Potentially Ciguatoxic Fish

- Schooling Jack Crevalle carnivorous: not tasty
- Solitary triggerfish herbivorous: very tasty
- Surgeonfish

Scombroid Fish Poisoning

- Agents: Toxic decomposition metabolites collectively called scombrottoxins; the scombrottoxins are not bioaccumulated dinoflagellate or diatom exotoxins.
- Toxins: Scombrottoxins = histamine and its primary N-methylhistamine metabolite, saurine.
- LD₅₀: No known human fatalities.
- Mechanism: Scombrottoxins form during gut bacteria-catalyzed, normothermic decarboxylation (*Proteus*, *Klebsiella*, *Lactobacillus*, *E. coli*, *Enterobacter* species) of muscle L-histidine in decomposing finfish dangling on commercial long lines or in underrefrigerated ship holes.
- Vectors: Paradoxically, non-scombroid fish are the most common food vectors of scombroid poisoning (amberjack, bonito, bluefish, mahi mahi, anchovies, sardines, herrings) > scombroid fish (albacore, cobia, tuna, mackerel, wahoo).
- Incubation: Minutes to 3–4 hours.
- Symptoms: Sudden warm facial flushing and “sunburn-like” rash, metallic-peppery taste, perioral burning and blistering sensations; then urticaria, pruritus, bronchospasm, palpitations, tachycardia, hypotension; fewer gastrointestinal symptoms of abdominal cramps, nausea, vomiting, and diarrhea.
- Diagnosis: Histidine-to-histamine spot indicator tests, thin-layer chromatography (TLC),

gas chromatography/mass spectrometry, high serum and urine histamine and saurine levels.

- Treatment: Severe poisoning—gastric emptying, then AC gut decontamination; otherwise, H₁- and H₂-blockers, β-agonists for bronchospasm with wheezing, and consider corticosteroids for allergic bronchospasm and urticaria/pruritus.
- Prognosis: Symptoms resolve in 12–24 hours even without treatment.
- Prevention: Patients on isoniazid (INH), a gastrointestinal histaminase inhibitor, are at increased risk; avoid nonrefrigerated and spoiling (pale gills) deep-sea fish; avoid seafood with histamine levels >50 mg/100 mg fish (FDA); regulate long-line fishing; require mandatory cold-chain (0°C) for all seafood from harvest until cooking/consumption.

Tetrodotoxic Fish Poisoning

- Agent: Endogenous toxin.
- Toxin: Endogenous toxin production by endosymbiotic gut bacteria (*Bacillus*, *Micrococcus*, *Acinetobacter*, *Altermonas*, *Vibrio*, and other enterobacterial species).
- LD₅₀ (IV in mice): 9 mcg/kg.
- Mechanism: Reversible binding to the outer pore of the Na channel, with decreased Na influx, preventing depolarization and subsequent nerve action potentials (NAPs).
- Vectors: All pufferfish (balloonfish, blowfish, fugu fish, globefish, swellfish, toadfish), porcupine fish, marine sunfish; xanthid crabs, marine worms; blue-ringed octopus bites; skin secretions of some newts, frogs, and toads.
- Incubation: 10–20 minutes.
- Symptoms: Initial paresthesias, perioral burning, then salivation, headache, nausea and vomiting (diarrhea rare), sweating, glove and stocking paresthesias then numbness, tremor, ataxia, dysarthria, dysphagia, respiratory depression then paralysis, cardiovascular instability, stupor, and coma.
- Diagnosis: Mouse bioassay, TLC, HPLC, gas chromatography/mass spectrometry.
- Treatment: Supportive = protect airway, gastric lavage then AC-MDAC, IV fluids, vasopressors, and mechanical ventilation.
- Prognosis: CFR = 62%; survivors will recover within 1 week of ICU care (not universally available, especially in developing world).

- Prevention: Avoid eating all pufferfish; travelers may consume fugu only in Japan, prepared by commercially licensed fugu chefs. Ban importation of all fugu fish and other pufferfish.

Miscellaneous Saltwater Fish Poisoning

- Shark poisoning: Consumption of cooked shark meat from large bull and tiger sharks has caused an initial ciguatera-like illness with perioral paresthesias, ataxia, and pruritus, then coma and death (increased CFR = 30%). Structure of two toxins (carchatoxins A and B) is unknown.
- Mackerel poisoning: Mild, self-limited diarrhea after consumption of cooked mackerel species due to a castor oil-like toxin. Mackerel liver consumption has also caused a hypervitaminosis-A-like syndrome with headache, nausea, vomiting, diarrhea, and a macular rash that later desquamates. A similar hypervitaminosis-A-like syndrome occurs after polar bear liver consumption and may cause pseudotumor cerebri.
- Mullet poisoning: Mild, self-limited intoxication with delusions, hallucinations, ataxia, and nightmares within minutes to hours after consumption of reef-schooling mullet. Toxin unidentified.

Freshwater Fish Poisoning

- Fish egg (fish roe) poisoning: Headache, nausea, vomiting, diarrhea, cold sweats, metallic taste, tinnitus, and syncope after the consumption of raw or cooked roe during the spawning season of several freshwater fish species including barbel, bream, carp, catfish, pike, salmon, and sturgeon. The uncharacterized toxin is probably a phospholipid egg-white nutrient. Prevention: avoid eating fish roe of high-risk species.
- Haff (Haff-Iuksov-Sartlen) disease: Paroxysmal myalgias and myospastic contractures with rhabdomyolysis and myoglobinuria (high levels of CPK) within 6–21 hours (mean 8 hours) of consuming cooked buffalo fish (*Ictiobus cypri-nellus*), or rarely (two cases) crayfish, from the Mississippi-Missouri River basin and similar basins (Volga-Caspian) worldwide. Primary source of endotoxin is unknown, with a CFR = 1%. Prevention: no buffalo fish consumption.

Marine Botulism

- Agent: *Clostridium botulinum* (marine).
- Toxin: Botulinum toxin, exclusively Type E, in decomposing marine mammals and seafood. Botulinum toxins include Types A–G, but Types A, B, and E (saltwater toxin) cause most human botulism cases.
- LD₅₀ (IV in mice): 0.0026 mcg/kg.
- Mechanism: Clostridial contamination of raw or improperly preserved seafood with exclusive production of botulinum toxin Type E on skin, in tissues, and muscle, particularly near gut.
- Vectors: All home-canned salt- or freshwater seafood, raw seafood, raw marine mammals, especially dolphin, seal, whale-muktuk (raw whale skin and underlying pink blubber).
- Incubation: ≤36 hours.
- Symptoms: Afebrile, weakness, oriented × 3, descending flaccid paralysis progressing to respiratory failure, cranial nerve (CN) palsies (blurred vision, diplopia, dysphagia, dysarthria), autonomic dysfunction (bradycardia, hypotension, nausea, vomiting, constipation > diarrhea).
- Diagnosis: Normal CSF, positive EMG, positive stool botulinum E toxin on mouse bioassay.
- Treatment: Polyvalent equine antitoxin, ICU support, mechanical ventilation.
- Prognosis: High CFR without ICU care.
- Prevention: Boil all raw or fermented Alaskan native dishes and home-canned seafoods ≥10 minutes before eating; notify state public health authority and CDC (for release provision of human botulinum antitoxin).

General Management Strategies

- Seek pathognomonic symptoms: Temperature reversal = ciguatera and sunburn-like rash = scombroid; submit fish samples to toxicology labs for TLC, HPLC, GC/MS.
- Protect airway and empty the stomach: Induce vomiting in witnessed ingestions only; orogastric lavage, then activated charcoal (AC). Avoid all cathartics.
- Provide supportive ICU care: IV fluids and vasopressors, mechanical ventilation.
- Consider specific pharmacotherapy: H₁- and H₂-blockers for scombroid; initial IV mannitol, then gabapentin po for neuropathic pain in ciguatera (untested).
- Notify public health authorities: In order to conduct epidemiologic outbreak analysis.

Prevention Strategies

- Monitor all harmful algal blooms (HABs): Use satellite and weather reports to predict red tides and issue timely seafood consumption advisories.
- Protect marine environments: Regulate drag-net and long-line commercial fishing; decrease atmospheric and deep-sea nuclear weapons testing; control crown-of-thorns starfish.
- Avoid consumption of well-known highly toxic species and any unrefrigerated or spoiled fish: Pufferfish = TTX; parrotfish and xanthid crabs = palytoxin; barracuda = ciguatoxin.
- Adhere to all regional seafood consumption advisories: If unavailable, seek advice from local health providers, hotel and tour operators.

Conclusions

- All shellfish, >300 finfish species, and marine mammals can cause poisoning with potent biological toxins and increased CFRs ranging from 1–62%. Example: botulinum toxin (botox) is #1, palytoxin is #2, TTX and saxitoxin are #5 among the living world's most potent biological toxins.
- Seafood toxins are not inactivated by cooking, smoking, salting, marinating, or freezing, and cannot be detected by human sight (pale gill color is very nonspecific), smell, or taste.
- Seafood poisonings affect the autonomic and central nervous systems and/or the gastrointestinal tract, causing symptoms ranging from mild gastrointestinal distress to fatal respiratory paralysis.
- Although the Food and Drug Administration monitors interstate sales, seafood is not federally inspected, and there are few available tests to assess seafood quality (e.g., Cigua-Check®), and few specific therapies to manage toxicity. Prevention is key!

Mushroom Poisonings

Chapter Outline

Descriptive epidemiology

Toxicological classification

- Cyclopeptide toxicity
- Gyromitrin toxicity
- Muscarine toxicity
- Coprine toxicity
- Ibotenic acid—muscimol
- Psilocybin toxicity
- Orellanine nephrotoxicity
- Miscellaneous gastrointestinal toxicity
- Lycoperdonosis

“Carefully” edible mushrooms: conclusions

Descriptive Epidemiology

- Incidence rate (United States): 5 mushroom poisonings per 100,000 persons per year.
- 95% of toxic mushrooms ingested cannot be identified.
- 50% of patients are asymptomatic, 25% require treatment, 15% of these have minor toxicity, 5% moderate toxicity, and 0.2% major toxicity.
- 1–2 patients die of mushroom poisoning each year (United States).
- 95% of deaths are due to *Amanita* species ingestions; case fatality rates (CFRs) for *Amanita* ingestions are 25–50%.

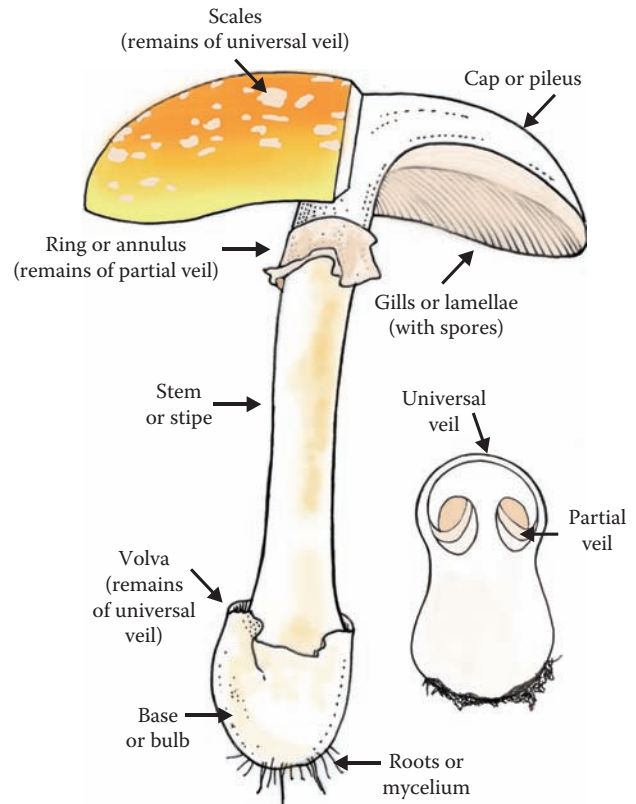


Figure 14.1 Anatomy of a mushroom. The anatomy of a poisonous mushroom, *Amanita muscaria* or fly amanita, with the juvenile mushroom button (right) and the mature adult mushroom or toadstool (left).

TABLE 14.1 An Onset Time and Target System Classification of Mushroom Poisoning by Common Mushroom Species

Early Onset Toxicity (<6 hours)	Late Onset Toxicity (within 6–24 hours)	Delayed Onset Toxicity (1 or more days)
Neurotoxic	Hepatotoxic	Nephrotoxic
Cholinergic: <i>Clitocybe</i> spp. (Funnel caps) <i>Inocybe</i> spp.	Amatotoxic: <i>Amanita</i> spp. <i>Galerina</i> spp. <i>Lepiota</i> spp.	Orellanine: <i>Cortinarius</i> spp. (Corts)
Glutaminergic: <i>Amanita muscaria</i> (Fly amanita) <i>Amanita pantherina</i> (Pantheramanita)	Nephrotoxic <i>Amanita proxima</i> <i>Amanita smithiana</i> (Toxic Lepidella)	Rhabdomyolytic <i>Tricholoma equestre</i> (Yellow trich) <i>Russula subnigricans</i> (Blackening Russula)
Epileptogenic: Gyromitra spp. (False morels)	Erythromelalgia <i>Clitocybe acromelalga</i> <i>Clitocybe amoenolens</i> (Poison dwarf bamboo mushroom)	Neurotoxic <i>Hapalopilus rustilans</i> (Purple-dye polypore)
Hallucinogenic: <i>Psilocybe</i> spp. (Mellow mushrooms)		
Allergic		
Immunohemolytic: <i>Paxillus involutus</i> (Poison Pax)		
Pneumonic: <i>Lycoperdon</i> spp. (Puffballs)		
Gastrointestinal (GI)		
Disulfiran reaction: <i>Coprinus atramentarius</i> (Alcohol inky caps)		
Miscellaneous GI: <i>Boletus</i> spp. <i>Chlorophyllum</i> spp. <i>Entoloma</i> spp.		

Toxicological Classification

- Cyclopeptide-containing mushrooms (potentially lethal hepatotoxicity)
- Monomethylhydrazine-containing mushrooms (B_6 -inhibitors, mimic isoniazid [INH] toxicity)
- Muscarine-containing mushrooms (muscarinic, cholinergic toxidrome)
- Coprine-containing mushrooms (“disulfiram reaction” following ethanol intake)
- Ibotenic acid–muscimol-containing mushrooms (GABA-nergic)
- Psilocybin-containing mushrooms (hallucinogenic, “mellow mushrooms”)
- Orellanine-containing mushrooms (nephrotoxic, oliguric renal failure)
- Miscellaneous gastrointestinal toxin-containing mushrooms (nonlethal nausea, vomiting, and diarrhea)
- Puffball poisoning or Lycoperdonosis (not a true poisoning, but extrinsic allergic asthma following spore inhalation)

Cyclopeptide Toxicity

- Representative genera: *Amanita*, *Galerina*, *Lepiota* species.
- Toxins: cyclopeptides = amatoxin > phallotoxin > virotoxin (nontoxic).
- Antidote: none specific, silibinin, penicillin G, thiocetic acid, cimetidine — inhibits CYP-450
- Diagnosis: Onset 6–10 hours; phase 1 — gastrointestinal toxicity — nausea, vomiting, diarrhea; phase 2 — liver function deteriorates; phase 3 — jaundice, liver failure, hepatorenal syndrome.
- Treatment: Supportive, liver transplant.

Gyromitrin (MMH) Toxicity

- Representative genus: *Gyromitra* species.
- Toxin: Gyromitrin, a monomethylhydrazine B_6 /GABA inhibitor.
- Antidote: B_6 or pyridoxine, 25 mg/kg IV.

- Diagnosis: Onset 6–10 hours; initial gastrointestinal symptoms, then seizures and hepatorenal failure, mimics INH toxicity.
- Treatment: Supportive, anticonvulsants.

Muscarine Toxicity

- Representative genera: All *Inocybe* and some *Clitocybe* species.
- Toxin: Muscarine.
- Antidote: Atropine, 1–2 mg/kg IV titrated to anticholinergic effects.
- Diagnosis: Onset 0.5–2 hours; symptoms — muscarinic cholinergic, SLUDE*, no CNS effects.
- Treatment: Supportive.

[*Salivation, lacrimation, urination, defecation, emesis.]

Coprine Toxicity

- Representative genus: *Coprinus* species.
- Toxin: Coprine.
- Antidote: None specific.
- Diagnosis: Onset 0.5–2 hours; disulfiram — reaction following ingestion of alcohol with facial flushing, nausea and vomiting, tachycardia, hypertension.
- Treatment: Supportive, IV fluids.

Ibotenic Acid — Muscimol

- Representative genus: *Amanita muscaria*, *A. pantherina*, *A. gemmata*.
- Toxins: Ibotenic acid and its primary metabolite, muscimol, a GABA-nergic glutamic acid analog.
- Antidote: None specific; benzodiazepines for convulsions.
- Diagnosis: Onset 0.5–2 hours; vertigo, somnolence, delirium, hallucinations; myoclonus and seizures in children.
- Treatment: Anticonvulsants (BZs).

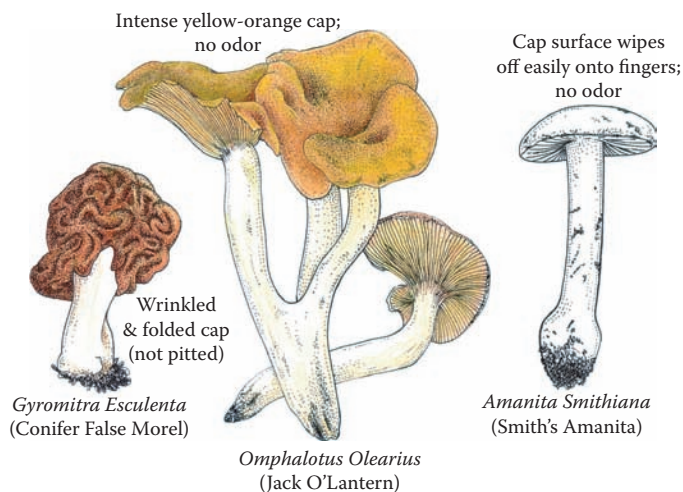


Figure 14.2a Study of three poisonous mushrooms. Study of three poisonous mushrooms and their unique identifying features. Left: *Gyromitra esculenta* (conifer false morel). Center: *Omphalotus clearius* (Jack O'Lantern). Right: *Amanita smithiana* (Smith's Amanita).

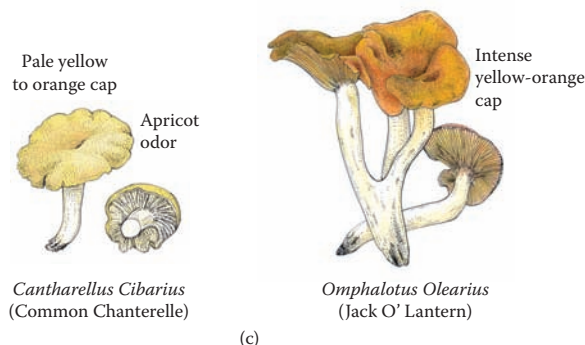
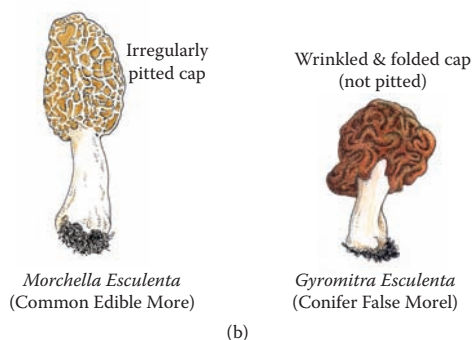
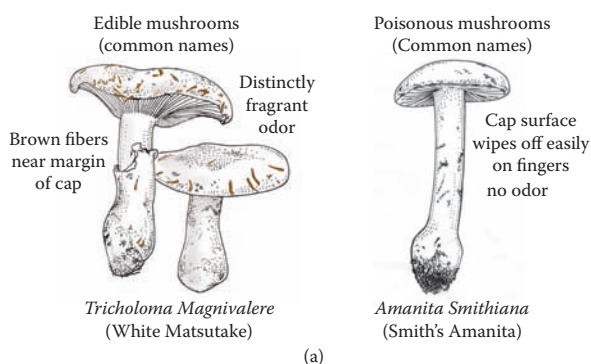


Figure 14.2b Study of edible and poisonous look-alike mushrooms. Some commonly confused look-alike mushrooms.



Figure 14.3 *Amanita muscaria* (fly amanita)-pink cap. A mature adult *Amanita muscaria* (fly amanita) characterized by its distinctive pinkish-red cap dotted with white scales, the remnants of the juvenile button's universal veil. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Forest Service Document, 1979, "Wild Mushrooms of North America.")



Figure 14.4 *Amanita muscaria* (fly amanita)-orange cap. Mature adult *Amanita muscaria* (fly amanita) characterized by orange caps rather than the more common pinkish-red caps. The caps are dotted with white scales, the remnants of the universal veils of juvenile buttons. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Forest Service Document, 1979, "Wild Mushrooms of North America.")

Psilocybin Toxicity

- Representative genus: *Psilocybe* species.
- Toxins: Psilocybin (serotonin agonist/antagonist) and psilocin indoles, both analogs of LSD.
- Antidote: None specific; benzodiazepines for convulsions.
- Diagnosis: Onset rapid 0.5–1 hour; hyperkinesis, ataxia, hallucinations.
- Treatment: Anticonvulsants.

Orellanine Nephrotoxicity

- Representative genera: *Cortinarius* spp.
- Toxins: Orellanine, a nephrotoxic bipyridyl.
- Antidote: None specific.
- Diagnosis: Initial gastrointestinal symptoms with headache and chills in 24–36 hours; then oliguric renal failure may develop days to weeks later.
- Treatment: Hemodialysis, renal transplant.



Figure 14.5 *Cortinarius collinitus* (deadly cort). Nephrotoxic *Cortinarius* species. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Forest Service Document, 1979, “Wild Mushrooms of North America.”)

Miscellaneous Gastrointestinal Toxicity

- Representative genera: Many miscellaneous species = *Boletes*, *Lactarius*, *Tricholoma*, *Chlorophyllum* species.
- Toxins: Ill-defined gastrointestinal toxins.
- Antidote: None specific.
- Diagnosis: Onset 0.5–3 hours; severe epigastric pain, nausea, vomiting, diarrhea, hypovolemic shock.
- Treatment: Supportive, fluids and electrolytes.

Lycoperdonosis

- Definition: Acute extrinsic allergic alveolitis following the inhalation of aerosolized puffball spores.
- Representative genus: *Lycoperdon* species puffballs.
- Toxins: Myco-allergens.
- Diagnosis: Onset rapid, in hours, acute nasopharyngitis, nausea, vomiting, inflammatory pneumonitis.
- Treatment: IV steroids, amphotericin B, mechanical ventilation.

“Carefully” Edible Mushrooms: Conclusions

- “There are old mushroom hunters, and bold mushroom hunters, but no old, bold mushroom hunters.”
- Avoid pure white mushrooms, little (and large) brown mushrooms, red- or pink-pored boletes (*Boletus* species), and all decomposing mushrooms.
- Cook all wild mushrooms. Cooking does not inactivate all mushroom toxins, and even edible mushrooms, if allowed to age or deteriorate, may become toxic.
- Select mushrooms at the grocery, not in the woods.



Figure 14.6 *Lepiota subclypeolaria* (amatotoxic lepiota). An amatoxin-containing poisonous *Lepiota* species mushroom. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Forest Service Document, 1979, "Wild Mushrooms of North America.")



Figure 14.8 *Lycoperdon candidum* (white puffballs). Common white puffballs (*Lycoperdon candidum*), release spores when crushed, which can cause acute bronchospasm or lycoperdonosis when inhaled. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Forest Service Document, 1979, "Wild Mushrooms of North America.")



Figure 14.7 *Morchella esculenta* (edible morel). The prized edible morel, *Morchella esculenta*, often confused with the poisonous false morel look-alike, *Gyromitra esculenta* (conifer false morel). (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Forest Service Document, 1979, "Wild Mushrooms of North America.") Also see Figure 14.2: Color diagram. Study of three poisonous mushrooms.

Poisonous Plants

Chapter Outline

Epidemiology of plant poisonings

Plant toxicology

Cardiovascular toxicity

Neurotoxicity group

Hepatotoxicity group

Cyanogenic group

Gastrointestinal toxicity

Dermatotoxicity group

Epidemiology of Plant Poisonings

- 10% of all calls to Poison Control Centers concern plant ingestion and toxicity.
- 80% of these calls involve children younger than age 6.
- Household plant poisonings are most common: 80% asymptomatic, <20% symptomatic, <7% hospital admits, Case Fatality Rate (CFR) = 0.001%.
- Outdoor plant ingestions are now increasing among adolescents and adults seeking hallucinogenic effects, and have greater toxicity than indoor plant ingestions.

TABLE 15.1 Common Plant Poisonings: United States

Botanical Name	Common Name	Primary Toxin
<i>Schefflera</i> species	Umbrella tree	Calcium oxalate
<i>Capsaicin</i> species	Chili pepper	Capsaicin
<i>Crassula</i> species	Jade plant	Calcium oxalate
<i>Diffenbachia</i>	Dumbcane	Calcium oxalate
<i>Euphoria</i> species	Poinsettia	Diterpenes
<i>Ilex</i> species	Holly	Triterpenes
<i>Philodendron</i>	Parlor ivy	Calcium oxalate
<i>Phytolacca</i>	Pokeweed	Phytolaccine
<i>Spathiphyllum</i>	Peace lily	Calcium oxalate
<i>Toxicodendron</i>	Poison ivy	Urushiol

TABLE 15.2 Lethal Plant Poisonings: United States

Botanical Name	Common Name	Primary Toxin
<i>Ricinus communis</i>	Castor bean	Ricin
<i>Abrus precatorius</i>	Jequirty pea	Abrin
<i>Conium maculatum</i>	Poison hemlock	Coniine
<i>Cicuta maculata</i>	Water hemlock	Cicutoxin
<i>Blighia sapida</i>	Ackee tree	Hypoglycin A
<i>Nerium oleander</i>	Oleander	Oleandrin ("digitalis")
<i>Convallaria majalis</i>	Lilly-of-the-Valley	Digitalis glycoside
<i>Urginea</i> species	Red squill	Scilliroside (cardiac glycoside)
<i>Digitalis</i> species	Foxglove	Digitalis glycoside
<i>Prunus</i> species	Almond, apricot	Amygdalin (cyanide)

Plant Toxicology

Cardiovascular Toxicity

- Cardiac glycoside group: Foxglove, common oleander, yellow oleander, lily-of-the valley, red squill.
- Aconitine group: Monkshood (wolfsbane).
- Grayanotoxin group: Rhododendron, azalea, mountain laurel.
- Nicotine group: Poison hemlock, tobacco.
- Belladonna alkaloids: Jimson weed, nightshade, Angel's trumpet, henbane, mandrake.



Figure 15.1 *Digitalis purpurea* (Foxglove). The cardiotoxic *Digitalis purpurea* (Foxglove) plant, a common garden flower, contains high concentrations of digitalis glycosides (*digitalis*, *digitoxigenin*), especially in its leaves. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, "Common Poisonous and Injurious Plants.")



Figure 15.2 *Convallaria majalis* (Lily-of-the-Valley). Like foxglove and oleander, *Convallaria majalis* (lily-of-the-valley), a common household plant, also contains cardiac glycosides that will heighten vagal tone and cardiac automaticity following ingestion. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, "Common Poisonous and Injurious Plants.")

Cardiac Glycosides

- Representative plants: Oleander, foxglove, red squill, lily-of-the-valley.
- Toxins: Digitalis, oleandrin, digitoxigenin: all inhibit the membrane-bound Na/K-ATPase pump increasing intracellular Na and Ca concentrations and extracellular (serum) K increasing automaticity, contractility, and vagal tone.
- Antidote: DigiBind® (digoxin-specific Fab).
- Diagnosis: Nausea, vomiting, dysrhythmias (bradydysrhythmias, heart blocks).
- Treatment: Gastrointestinal decontamination (lavage and AC), monitor ECG and digitalis (digoxin) levels.

Aconitine Group

- Representative plants: Monkshood (wolfsbane).
- Toxin: Parasympathomimetic terpene and aconitine alkaloids cause prolonged opening of cardiac Na channels with increased vagomimesis



Figure 15.3 *Aconitum napellus* (Monkshood). *Aconitum napellus* (monkshood), so named for its purple flower that resembles a helmet or monk's hood, contains the cardiotoxin, aconitine, which prolongs the opening of cardiac sodium channels inducing ventricular dysrhythmias. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, "Common Poisonous and Injurious Plants".)

and ventricular automaticity, similar to digitalis effects.

- Antidote: None.
- Diagnosis: Nausea, vomiting, diarrhea, paresthesias, atrioventricular block, ventricular tachycardia, ventricular fibrillation, respiratory failure.
- Treatment: Gastrointestinal decontamination (lavage and AC), temporary pacemaker, aconitine is not bound by digoxin Fab.

Grayanotoxins

- Representative plants: Azalea, rhododendron, mountain laurel, and local honey containing plant nectar.
- Toxins: Parasympathomimetic oily diterpene — grayanotoxins force open cardiac Na channels increasing cardiac automaticity and enhancing vagal tone, similar to digitalis effects.
- Antidote: None.
- Diagnosis: Gastrointestinal symptoms, SLUDE syndrome (salivation, lacrimation, urination, defecation, emesis) or DUMBELS syndrome (diarrhea, urination, miosis, bronchospasm, bronchorrhea, emesis, lacrimation, salivation), weakness, bradydysrhythmias, ataxia, paresthesias, seizures.

- Treatment: Gastrointestinal decontamination (lavage and activated charcoal [AC]); grayanotoxins do not bind to digoxin Fabs.

Nicotine Group

- Representative plants: Poison hemlock (Socrates) — resembles Queen Anne's lace (wild carrot) and wild tobacco.
- Toxin: Coniine, a nicotine alkaloid, blocks coniine nicotinic cholinergic receptors.
- Antidote: None.
- Diagnosis: Initial salivation, nausea, vomiting and diarrhea; then diaphoresis, tachycardia, tremors, seiwzures, ascending paralysis, respiratory failure, coma.
- Treatment: Gastrointestinal decontamination (lavage and AC).

Belladonna Alkaloids

- Representative plants: Nightshade, jessamine, jimson weed (thornapple), *Brugmansia* and *Solandra* species (Angel's trumpet).
- Toxins: Atropine = its plant isomer is hyoscyamine; scopolamine = its plant isomer is hyoscine.
- Antidote: Physostigmine for CNS effects.



Figure 15.4 *Conium maculatum* (Poison hemlock). *Conium Maculatum* (poison hemlock) resembles common herbs, such as wild carrot and Queen Anne's lace, and contains the nicotinic receptor blocker, coniine, which induces seizures and paralysis on ingestion. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, "Common Poisonous and Injurious Plants".)



Figure 15.5 *Nicotiana glauca* (Wild Tree Tobacco). Like poison hemlock, *Nicotiana glauca* or wild tobacco contains epileptogenic nicotine-like alkaloids. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, "Common Poisonous and Injurious Plants.")



Figure 15.6 *Laburnum anagyroides* (Goldenchain) 1. *Laburnum anagyroides* or golden chain also contains nicotine-like alkaloids, which can induce headache, ataxia, and seizures with respiratory arrest on ingestion. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, "Common Poisonous and Injurious Plants.")

- Diagnosis: Atropine toxicity = fever, dry mouth, tachycardia, ileus, urinary retention, hallucinations, seizures, "red as a beet, hot as Hades, dry as a bone, mad as a hatter."
- Treatment: Gastrointestinal decontamination.



Figure 15.7 *Nerium oleander* (dogbane). All parts of the oleander shrub are highly toxic and contain digitalis glycosides that can cause nausea, vomiting, tachyarrhythmias, and cardiac conduction disturbances, including complete heart block, on ingestion. Oleander grows up to 9 meters tall in warm beachfront locations and produces abundant white, yellow, pink, or red flowers. Oleander has poisoned beach-goers who have selected oleander branches to use as skewers to roast their hot dogs over beachside bonfires. Source: Department of the Army, The Illustrated Field Guide to Edible Wild Plants, 2003.



Figure 15.8 *Datura stramonium* (Jimson Weed or Thornapple). The belladonna alkaloid-containing jimson weed or thornapple plant (*Datura stramonium*). Legend holds that early American colonists encouraged occupying British troops to consume salads of local "jimson" (for Jamestown, Virginia) weed and to suffer the central and peripheral anticholinergic consequences (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, "Common Poisonous and Injurious Plants.")



Figure 15.9 Angel's Trumpet (*Brugmasia* spp. as shown and *Solandra* spp.). The angel's trumpet plants, *Brugmasia* spp. (shown) and *Solandra* spp. (not shown) are very common perennials in the Southern US, and contain a scopolamine-like belladonna alkaloid that can cause a central anticholinergic syndrome on ingestion. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, "Common Poisonous and Injurious Plants.")



Figure 15.10 Commercial Landscaping with Angel's Trumpet (*Brugmasia sauveolens*), San Diego, CA.: The angel's trumpet plant was introduced into the temperate and tropical areas of the U.S. from southeastern Brazil for landscaping purposes. All parts of the plants are toxic and contain a combination of several anticholinergic tropine alkaloids, including atropine, hyoscyamine, and scopolamine. Since the 1990s, there have been increasing U.S. reports of central anticholinergic syndromes following the ingestion of teas and potions made from angel's trumpet in adolescents seeking legal hallucinogens.

Neurotoxicity Group

Convulsants

- Representative plants: Water hemlock, also resembles the edible herb Queen Anne's lace (wild carrot).
- Toxin: Cicutoxin.
- Antidote: None.
- Diagnosis: Diaphoresis, nausea, vomiting, and abdominal cramps within 1 hour; then severe convulsions = status epilepticus, case fatality rate (CFR) 30%.
- Treatment: Gastrointestinal decontamination (lavage and AC), anticonvulsants (barbiturates, benzodiazepines).

Hallucinogens

- Representative plants: Morning glory ("LSD," contains "LSD-like" substance), peyote cactus, nutmeg and mace (powdered spice made by grinding nutmeg kernels).
- Nutmeg and mace: (*Myristica fragrans*, resembles methylene dioxymethamphetamine (MDMA) = *Ecstasy* toxicity).
- Toxins: Morning glory: lysergamide (LSD-like); peyote: mescaline; and nutmeg and mace: myristicin (MDMA-like).
- Antidote: None.
- Diagnosis: Initial nausea and vomiting, diaphoresis, mental status change, deep sleep (nutmeg), hallucinations.
- Treatment: Gastrointestinal decontamination, supportive.

Hepatotoxicity Group

Ackee

- Representative plant: Ackee tree and its fruit (*Blighia sapida*) common in South Florida and the Caribbean.
- Toxins: Hypoglycins A and B-inhibit glucose-6-phosphate dehydrogenase (G-6-PD) blocking hydrolysis of fatty acids and cause *Jamaican vomiting sickness*.
- Antidote: 50% dextrose.
- Diagnosis: Severe nausea and vomiting, hypoglycemia, hyperammonemia, mental status changes, hypothermia, metabolic acidosis, seizures, deteriorating liver function-centrilobular hepatic necrosis.
- Treatment: Gastrointestinal decontamination (lavage and AC).

Comfrey, Sassafras

- Representative plants: Comfrey, sassafras (gumbo file powder).
- Toxins: Hepatotoxic pyrrolizidine alkaloids and safrole respectively.
- Antidote: None.
- Diagnosis: Hepatotoxicity, specifically hepatic veno-occlusive disease (comfrey), and, possibly, hepatocellular carcinoma (sassafras).
- Treatment: Gastrointestinal decontamination (lavage and AC).

Cyanogenic Group

- Representative plants: *Prunus* species, especially seeds of almond, apple, apricot, plum, peach, and cherry; also elderberry, hydrangea.
- Toxin: Amygdalin, which is hydrolyzed to hydrocyanic acid (HCN) = Laetrile®, an illicit cancer chemotherapeutic made from apricot pits and containing amygdalin.
- Antidote: Lilly cyanide kit®: inhaled amyl nitrite, IV sodium nitrite, and IV sodium thiosulfate.
- Diagnosis: headache, dizziness, vertigo, seizures, hyperthermia, stupor, coma.
- Treatment: Gastrointestinal decontamination.



Figure 15.11 *Cicuta maculata* (Water Hemlock). *Cicuta maculata* or water hemlock grows ubiquitously on riverbanks, resembles edible herbs, and contains cicutoxin, which can induce seizures and rhabdomyolysis following ingestion. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, "Common Poisonous and Injurious Plants.")

Gastrointestinal Toxicity

Calcium Oxalate

- Representative plants: Species of *Diffenbachia*, *Philodendron*, *Brassaia*, *Schefflera*, *Pothos*, *Caladium*, *Spathiphyllum*.
- Toxin: Calcium oxalate crystals bundled in raphides and loaded into idioblasts to be fired with additional proteolytic enzymes. Example: *Diffenbachia*.
- Antidote: None.
- Diagnosis: Salivation, dysphagia, dysarthria, mucosal edema and oral bullae, contact dermatitis and conjunctivitis.
- Treatment: Cold milk/ice, ice cream; consider corticosteroids.

Probably Calcium Oxalate

The jade plant (*Crassula argentea*) is a very popular houseplant from which no toxin has been isolated, yet there is a case report of a 1-year-old who ingested several leaves and had persistent diarrhea and perianal dermatitis (Schilling et al., *Vet. Hum. Toxicity*, 1980).



Figure 15.12 Dumbcane (*Diffenbachia* spp.). *Diffenbachia* or dumbcane is a popular household decorative plant whose leaves contain idioblasts that discharge irritant calcium oxalate crystals when damaged. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, "Common Poisonous and Injurious Plants.")



Figure 15.14 *Ricinus communis* (Castor Bean Plant). The castor bean plant, *Ricinus communis*, is the source of the ricin-containing castor bean seed. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, "Common Poisonous and Injurious Plants.")



Figure 15.13 *Philodendron* spp. Caption: Like *Diffenbachia* or dumbcane, philodendrons, caladiums, and pothos are all also very popular indoor decorative plants whose leaves contain idioblasts that discharge irritant calcium oxalate crystals when damaged, causing salivation and oropharyngeal edema. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, "Common Poisonous and Injurious Plants.")



Figure 15.15 *Abrus precatorius* (Rosary or Jequirty Pea): Seeds in Pods. *Abrus precatorius* (the rosary or jequirty pea) is a tropical shrub, whose seeds contain the toxalbumin, abrin, which can induce hemorrhagic gastroenteritis following chewing and ingestion of seeds. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, "Common Poisonous and Injurious Plants.")

Toxalbumins

- Representative plants: Castor bean, jequirty (rosary) pea, black locust.
- Toxins: Ricin (castor bean), abrin (rosary pea) — protein synthesis inhibitors, rapid cell death (especially in gastrointestinal tract).
- Antidote: None.
- Diagnosis: Severe hemorrhagic gastroenteritis, hematochezia, seizures, CNS depression, cerebral edema, hepatorenal failure.
- Treatment: Gastrointestinal decontamination, whole-bowel irrigation.

Solanine Group

- Representative plants: Leaves of green potatoes (especially potato “eyes” and vines) and tomatoes (leaves and stems).
- Toxins: Solanine, solanidine.
- Antidote: None.
- Diagnosis: Within 2–24 hours, nausea, vomiting, diarrhea, abdominal cramps; later delirium, hallucinations, coma, death, no deaths since 1960s.
- Treatment: Gastrointestinal decontamination (lavage and AC).

Colchicine Group

- Representative plants: Autumn crocus, glory lily.
- Toxin: Colchicine.
- Antidote: Colchicine Fabs.
- Diagnosis: Nausea, vomiting, bloody diarrhea, agranulocytosis due to mitosis inhibition, alopecia.
- Treatment: Gastrointestinal decontamination (lavage and AC).

Christmas Group

- Representative plants: Mistletoe, holly, poinsettia.
- Toxins: Miscellaneous diterpene esters.
- Antidote: None.
- Diagnosis: Nausea, vomiting, abdominal cramps, oral mucosal burns; last death due to poinsettia ingestion — Hawaii, 1919.
- Treatment: Gastrointestinal decontamination (lavage and AC).

Miscellaneous

- Representative plants: Pokeweed, English ivy, yew, horse chestnut.
- Toxin: Phytolaccine (phytolaccatoxin), phytolaccagenin.
- Antidote: None.
- Diagnosis: Nausea, vomiting, diarrhea, abdominal cramps — colic, lymphocytosis (pokeweed).



Figure 15.16 *Abrus* (Rosary Pea): Seeds. Rosary pea seeds are still used in the Caribbean tropics to make colorful jewelry and rosaries, and may be swallowed whole without serious gastrointestinal toxicity. On the other hand, chewing the seeds can release the protein synthesis inhibitor, abrin, which, like ricin, can cause delayed hemorrhagic gastroenteritis with hypovolemic dehydration and high case fatality. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, “Common Poisonous and Injurious Plants.”)



Figure 15.17 *Euphorbia marginata* (Snow-on-the-Mountain). The *Euphorbia* species plants include a wide variety of popularly cultivated indoor and outdoor plants, specifically poinsettias, candelabra and pencil cactus, creeping spurge, and snow-on-the-mountain. The *Euphorbia* species plants can induce a chemical dermatitis on contact with their milky sap or cause mild gastroenteritis on ingestion. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, “Common Poisonous and Injurious Plants.”)

Dermatotoxicity Group

Toxicodendron

- Representative plants: *Rhus* family = poison ivy, poison oak, poison sumac. “Leaves of three, let them be.”
- Toxin: The active toxin, urushiol, is suspended in the oily and sticky resin, toxicodendrol, of all *Rhus* family plants.
- Antidote: None.
- Diagnosis: Pruritic linear vesiculobullous dermatitis.
- Treatment: Antihistamines, topical-systemic steroids.



Figure 15.18 *Taxus* spp. (Yew spp.). Shrub. One of the many varieties of yew shrub or tree that contains taxine, a cardiac sodium-potassium channel blocker that can cause cardiac arrest on ingestion. The anticancer drug, tamoxifen, is derived from a *Taxus* spp. Shrub or tree, the Pacific yew. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, “Common Poisonous and Injurious Plants.”)



Figure 15.19 *Toxicodendron radicans* (Poison Ivy): Leaves. The *Toxicodendron* group of vines and shrubs can induce severe chemical contact dermatitis on exposure to their oily resin, toxicodendrol, which contains the suspended active toxin, urushiol. The *Toxicodendron* group of plants includes poison ivy as shown (*Toxicodendron radicans*), poison oak (*Toxicodendron toxicarium*), and poison sumac (*Toxicodendron vernix*). Note poison ivy’s cluster of three leaves on red stems. (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, “Common Poisonous and Injurious Plants.”)



Figure 15.20 *Toxicodendron radicans* (Poison Ivy): Vine. The *Toxicodendron* plants may resemble perennial ivy vines, low growing shrubs (poison oak), or small trees (poison sumac). (Courtesy of Charles P. Sea, M.D., Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Health and Human Services, 1981, “Common Poisonous and Injurious Plants.”)

TABLE 15.3 Dermatotoxicity Group

Allergic Contact Dermatitis	Allergic Contact Urticaria	Phytophotodermatitis (Due to Sunlight-Activated Psoralens)
Poison ivy	Stinging nettle	Celery
Poison oak	Wood nettle	Figs
Poison sumac	Bull nettle	Limes
Ginkgo	Agavé (Century cactus)	Cow parsnip
Mango	Primrose	Wild parsnip

Terrestrial Envenomings

Chapter Outline

Terrestrial animals

- Reptiles
- Amphibians

Arthropods (insects)

- Arachnids
- Tick paralysis
- Vespid
- Lepidoptera species
- Miscellaneous

Terrestrial Animals

Reptiles

Non-Poisonous Snakes as Pets

Major Problems with “Harmless” Snakes

- Family Colubridae (United States) considered nonvenomous and harmless, yet capable of inflicting contaminated bite wounds. There are many venomous Colubrids in Africa and Asia, including the Boomslang and the bird or twig snake.
- Reptilian *Salmonella* species — *Salmonella* sepsis in infants and elderly with high case fatality rates (CFRs).
- Grooved teeth break off and deliver “venom” in bites.
- Toxic venoms = Duvernoy’s glands in species once thought “harmless” may actually be venomous. Examples: hognose, garter, ringneck, parrot snakes.
- Treatment: Tetanus toxoid and antibiotics.



Figure 16.1 Southeastern Copperhead (*Agkistrodon contortrix contortrix*). Southeastern copperhead (*Agkistrodon contortrix contortrix*), photographed in Southeast Louisiana. Copperheads are commonly encountered venomous crotalid pit vipers in the southeastern U.S. (Courtesy of Dino Ferri, Herpetologist and Assistant Curator of Reptiles and Amphibians, Audubon Nature Institute, New Orleans, LA.)

Crotalids: Pit Vipers

Southern Copperhead

- Latin: *Agkistrodon contortrix*.
- Venom: nucleic acid/acetylcholinesterases, serotonin (5-HT), kinins, phospholipases, collagenase, hyaluronidase — a “mosaic of antigens.”
- Diagnosis: Hemorrhagic blisters, proximal edema, minimal systemic toxicity.
- Antidote: Crotalidae polyvalent antivenom (CPA) now replaced by crotalid-specific F-antibody fragments (Fabs) antivenom (CroFAB®).
- Treatment: Tetanus toxoid, antibiotics (cephalosporins > penicillin), conservative wound management.

Crotalids: Copperhead Bite

- Copperhead bite, minimum envenomation, no CroFAB®. Tetanus prophylaxis. Consider antibiotic coverage with a cephalosporin.

Eastern Cottonmouth (Water Moccasin)

- Latin: *Agkistrodon piscivorus piscivorus*.
- Venom: A “mosaic of antigens” similar to copperhead components.
- Diagnosis: Slightly more severe envenomations than copperhead bites.
- Antidote: CroFAB® rarely indicated.
- Treatment: Same as copperhead.

Crotalids: Vipers/Rattlesnakes

Eastern Diamondback

- Latin: *Crotalus adamanteus*.
- Venom: “Mosaic of antigens.”
- Diagnosis: Hemorrhagic bullae, tissue necrosis, massive edema, nausea and vomiting, cardiovascular instability, pseudo- and true-disseminated intravascular coagulation (DIC), hemolysis, acute renal failure (ARF). Pseudo-DIC is caused



Figure 16.2 Eastern Diamondback Rattlesnake (*Crotalus adamanteus*), Bienville Parish, Louisiana. A non-retreating Eastern Diamondback Rattlesnake (*Crotalus adamanteus*) poised to strike and photographed in Bienville Parish, LA. (Courtesy of Dino Ferri, Herpetologist and Assistant Curator of Reptiles and Amphibians, Audubon Nature Institute, New Orleans, LA.)

by a thrombin-like enzyme in crotalid venom that incompletely cleaves the fibrinopeptides A and B off fibrinogen and fails to activate platelet factor XIII. This results in elevated fibrin split products and unstable clots and not in platelet and clotting factor consumption as in true DIC.

- Antidote: Moderate envenomations — 5 to 10 vials; severe envenomations — 10 to 40 vials CroFAB®.
- Treatment: Immobilize limb, no ice, tetanus toxoid, antibiotics, pressors, blood products, wound debride, rarely fasciotomy.

Canebrake Rattler

- Latin: *Crotalus horridus atricaudatus*.
- Venom: Same as diamondback.
- Diagnosis: Same as diamondback.
- Treatment: Same.

Mojave Rattler

- Latin: *Crotalus scutulatus scutulatus*.
- Venom: Potent neurotoxins, capable of causing respiratory paralysis, fewer tissue-destructive antigens.



Figure 16.3 Northern Pacific Rattlesnake (*Crotalus viridis oreganus*), American Pacific Northwest. The Northern Pacific Rattlesnake (*Crotalus viridis oreganus*) is one of many regional species of crotalid rattlesnakes in North America



Figure 16.4 The Eastern Massasauga or Pygmy Rattlesnake (*Sistrurus catenatus catenatus*). The Eastern Massasauga or Pygmy Rattlesnakes (*Sistrurus catenatus catenatus*) are significantly smaller than the *Crotalus* species rattlesnakes, but can still inflict envenoming snakebites. (Courtesy of Charles P. Sea, Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA.)

- Diagnosis: Minor local symptoms, delayed neurotoxicity — lethargy, obtundation, cranial nerve palsies, weakness, respiratory paralysis, rarely coagulopathy.
- Antidote: Early CroFAB® — at least 10 vials, not effective in reversing neurotoxicity.
- Treatment: Tetanus toxoid, antibiotics.

Eastern Massasauga (Pygmy Rattlesnakes)

- Latin: *Sistrurus catenatus catenatus*.
- Venom: “Mosaic of antigens.”
- Diagnosis: Same as diamondback, but not as serious.
- Antidote: Moderate–severe envenomation — 5 to 20 vials CroFAB®.
- Treatment: Same as diamondback bites.

Elapids: Coral Snakes in the United States

Neurotoxic elapids also include the African and Asian cobras, African mambas, Asian kraits, and the major venomous snakes of Australia — Taipan, tiger snake, brown snake, death adder.

Eastern Coral Snake

- Latin: *Micrurus fulvius fulvius*.
- Venom: Neurotoxin.
- Diagnosis: Shy, docile, nocturnal, bites/chews when disturbed, few local symptoms 12–24 hours later — paresis, paresthesias, fasciculations, first at bite site, then more generalized; dysarthria, dysphagia, ptosis, stridor, diplopia, respiratory arrest.
- Antidote: Equine bivalent (Eastern + Texas coral snakes) — elapid antivenom 5 to 10 vials.
- Treatment: Mechanical ventilation required in 15%.

Texas (Western) Coral Snake

- Latin: *Micrurus fulvius tenere* (Texas).
- Venom: Delayed neurotoxin.
- Diagnosis: Same as Eastern coral.
- Antidote: Equine elapid bivalent antivenom.
- Treatment: Mandatory admit as for eastern coral snake bites.

Sonoran Coral Snake (Arizona, Mexico, Central and South America)

- Latin: *Micruroides euryxanthus*.
- Venom: Less potent, delayed neurotoxin.
- Diagnosis: Less severe neurotoxicity.

- Antidote: None available; only bivalent Elapid antivenom from eastern and Texas coral snakes.
- Treatment: Supportive, observe for apnea and respiratory failure for 24 hours.



Figure 16.5 Central American Coral Snake (*Micrurus alleni*), Osa Peninsula, Costa Rica. North and Central American *Micrurus* species Coral Snakes are all brightly colored, docile and nocturnal, and may rarely inflict neurotoxic snakebites, especially if handled. (Courtesy of Dino Ferri, Herpetologist and Assistant Curator of Reptiles and Amphibians, Audubon Nature Institute, New Orleans, LA.)

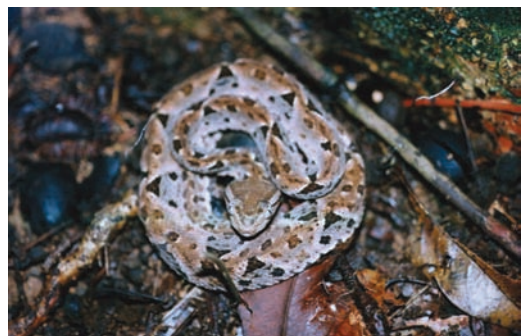


Figure 16.6 Latin American Fer-de-Lance (*Bothrops asper*), Northern Costa Rica. Bothrops species, such as the Fer-de-Lance (*Bothrops asper*), account for many of the seriously envenoming snakebites in tropical Latin America. Note the distinct triangular or lance-like head. (Courtesy of Dino Ferri, Herpetologist and Assistant Curator of Reptiles and Amphibians, Audubon Nature Institute, New Orleans, LA.)



Figure 16.7 *Porthidium ophyromegas*, formerly *Bothrops orphyromegas*, Northwestern Costa Rica. *Porthidium* species venomous snakebites are relatively common in tropical Central America and northern South America, but fatalities are exceedingly rare. (Courtesy of Dino Ferri, Herpetologist and Assistant Curator of Reptiles and Amphibians, Audubon Nature Institute, New Orleans, LA.)

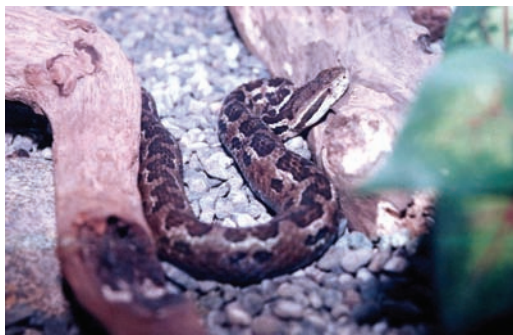


Figure 16.8 *Porthidium nasutum*, Northwestern Costa Rica. *Porthidium*, formerly *Bothrops*, species snakes are not as aggressive when disturbed as the *Bothrops* species, such as the Fer-de-Lance, but still capable of inflicting mildly to moderately envenoming snakebites. (Courtesy of Dino Ferri, Herpetologist and Assistant Curator of Reptiles and Amphibians, Audubon Nature Institute, New Orleans, LA.)

Contraindicated Snake Bite Treatments (United States)

- Tourniquets — lymphatic constriction bands are also not highly recommended in the United States.
- Ice packs or immersion — potential for frostbite.
- Excision of bite site.
- Electric shock to bite site.
- Cutting on bite site to extract venom — negative-pressure venom extractors have been used on some exotic snake bite sites.
- Sucking on the bite site — further contaminates wound.

Lizards: Order Squamata

Gila Monster

- Latin: *Heloderma suspectum*.
- Venom: Similar to crotalid venoms, but even more complex with kallekrein, and helothermine; open grooved teeth and no fangs make venom delivery inefficient.
- Diagnosis: Shy, slow, nocturnal creatures capable of inflicting venom delivery apparatus — macerating bites, with surrounding cyanosis + edema, respiratory depression possible, anaphylaxis, coagulopathy, and, possibly, myocardial infarction.
- Antidote: None, no antivenom.
- Treatment: Supportive.



Figure 16.9 Gila Monster (*Heloderma suspectum*), Desert Southwest U.S. The shy, slow-moving, and nocturnally active Gila Monster (*Heloderma suspectum*), once a very common inhabitant of the American desert Southwest, may rarely inflict painful, macerating, envenoming bite, especially if handled. Venom injection is inefficiently delivered by grooved teeth that communicated with poison glands and not by fangs as in pit vipers. *Heloderma* species (*H. suspectum*, *H. horridum*) lizard venoms are complex in chemical composition and may induce anaphylaxis, respiratory depression, and coagulopathy. There is no antivenom available in the U.S., and treatment of envenoming bites is supportive. (Courtesy of Dino Ferri, Herpetologist and Assistant Curator of Reptiles and Amphibians, Audubon Nature Institute, New Orleans, LA.)

Mexican Beaded Lizard

- Latin: *Heloderma horridum*.
- Venom: Same as Gila monster.
- Diagnosis: Same as Gila monster, but less severe systemic effects.
- Antidote: None, no antivenom.
- Treatment: Same as for Gila monster bite, supportive, aggressive wound management, tetanus toxoid, antibiotics.

Amphibians

Newts and Salamanders

Oregon (Western) Rough-Skinned Newt

- Latin: *Taricha granulose*.
- Venom: Secretes neurotoxic tetrodotoxins (same as pufferfish — Japanese fugu fish and blue-ringed octopus) through skin.
- Diagnosis: Neurotoxicity seen following ingestion and potentially following contact; tetrodotoxin poisoning = perioral burning and paresthesias, salivation, sweating, headache, nausea, vomiting, dysphagia, dysarthria, numbness, dyspnea, respiratory depression, neuromuscular paralysis ingestion.
- Antidote: None.
- Treatment: Supportive.

Salamandra Species Salamanders

- Latin: *Salamandra* species.
- Venom: Potent CNS neurotoxin — salamandrin.
- Diagnosis: Neurotoxicity; paresthesias, weakness, ataxia.
- Antidote: None.
- Treatment: Supportive.

Toads

Colorado River Toad

- Latin: *Bufo alvarius*.
- Venom: Skin-secreted biogenic amines that are serotonin-agonists and cause LSD-like hallucinations.
- Diagnosis: Hallucinations after toad licking and eating toad soup; accompanied by salivation, euphoria, seizures, dysrhythmias.
- Antidote: None.
- Treatment: Supportive.

Cane Toad

- Latin: *Bufo marinus*.
- Venom: Bufotoxins — considered by Chinese as aphrodisiacs (bufadienolides > bufotalins and bufotenines), all are cardiac glycosides and resemble digoxin in toxicity.
- Diagnosis: “Dig-toxic” patients manifesting nausea, vomiting, bradycardia, dysrhythmias, hyperkalemia.
- Antidote: DigiBind® (Dig Fab antibodies).
- Treatment: Management of digoxin-like toxicity, maintain diuresis and monitor K⁺ levels. Calcium administration is contraindicated.

Arthropods (Insects)

Arachnids (spiders)

Latrodectus

Black Widow, Red Hourglass Spider

- Latin: *Latrodectus mactans*.
- Venom: alpha-Latrotoxin causes presynaptic stimulation and neurotransmitter — containing vesicle exocytosis at all motor end plates releasing acetylcholine, epinephrine, and gamma-aminobutyric acid (GABA). Also opens ion channels in motor end plates allowing a massive influx of calcium ions.
- Diagnosis: Two painful red spots within hours — latrodectism = *facies latrodectismica*, nausea, vomiting, salivation, urine retention, priapism, bronchorrhea, abdominal muscle cramps — rigidity, tachycardia, hypertension, restlessness, seizures.



Figure 16.10a Female Black Widow Spider (*Latrodectus mactans*). The venom of the Black Widow spider (*Latrodectus mactans*) contains alpha-latrotoxin, a neurotoxin that causes presynaptic stimulation of adrenergic and cholinergic receptors. (Courtesy of Charles P. Sea, Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA.)

- Latin: *Latrodectus mactans*.
- Antidote: *Latrodectus mactans* antivenom — a crude monovalent hyperimmune horse serum (IgG) antivenom.
- Treatment: Tetanus toxoid, cold packs, benzodiazepines preferred over calcium gluconate for cramps and abdominal muscle spasms.



Figure 16.10b Female Black Widow Spider (*Latrodectus mactans*), Ventral View. Note the dark red patterns on the ventral abdomen of the female black widow spider, particularly the characteristic hourglass pattern. Female black widow spiders may display a variety of colors and patterns on their ventral abdomens ranging in colors from orange to reddish black and in patterns from splotchy circles to triangles. (Courtesy of Zach Lemann, Entomologist/Arachnologist, Audubon Nature Institute, New Orleans, LA.)

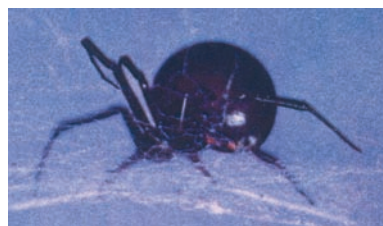


Figure 16.10c Female Black Widow Spider (*Latrodectus mactans*), Lateral View. The characteristic ventral markings on the female black widow spider (*Latrodectus mactans*) are not clearly visible from lateral and dorsal vantages and only the size and shiny black color identify the spider as *Latrodectus mactans*. (Courtesy of Zach Lemann, Entomologist/Arachnologist, Audubon Nature Institute, New Orleans, LA.)

Loxosceles

Brown Recluse

- Latin: *Loxosceles reclusa*.
- Venom: Sphingomyelinase D primarily, also includes proteases, esterases, phospholipases, hyaluronidase, collagenase, and dermonecrosis factors 33 and 37.
- Diagnosis: Painless bite, bleeding blister within 2 hours, necrotic ulcer, and regional edema (necrotic araneism) by 8 hours, eschar — 1 week, local then systemic DIC-methemoglobinemia, thrombocytopenia, hemolysis — acute renal failure (ARF). Systemic loxoscelism = fever, nausea, chills, rash, arthralgias, seizures, coma.
- Antidote: Experimental rabbit hyperimmune antivenom, not commercially available.
- Treatment: Tetanus toxoid, consider antibiotics, wound care, conservative surgical debridement, consider hyperbaric O₂, consider leukocyte (pmn) microtubule inhibitors = dapsone (can cause hemolysis in G-6-PD deficiency) and colchicines.

Hobo Spider

Hobo Spider, Aggressive House Spider
(recent European immigrant to
Northwest United States — Wash-
ington and Oregon)

- Latin: *Tegenaria agrestis*.
- Venom: Locally cytotoxic venom similar to brown recluse venom that may cause necrotic araneism.
- Exception: Males more aggressive and venomous than females and cause more bites.
- Diagnosis: Initial painless bite, expanding erythema within hours, blistering within 15–35 hours, necrotic ulcer-eschar, sloughs with scar over months and years. Complications: nausea, vomiting, diarrhea, aplastic anemia, and possible death, yet very rare.
- Antidote: None.
- Treatment: Tetanus toxoid, wound care, skin graft; consider systemic steroids.



Figure 16.11a Female Brown Recluse Spider (*Loxosceles reclusa*). The venom of the Brown Recluse spider contains sphingomyelinase-D that can induce cytotoxic tissue necrosis surrounding bite sites. (Courtesy of Charles P. Sea, Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, U.S. Department of Agriculture Document # 556, 1972, "Controlling the Brown Recluse Spider.")



Figure 16.11b Female Brown Recluse Spider (*Loxosceles reclusa*) Building Her Web. The female brown recluse prefers a dark corner or crevice, where a floor meets a wall or behind a cabinet or picture, to construct a messy web of crossed threads rather than a geometric orb, characteristic of the mildly envenoming orb-weaving *Araneus* and *Neosconus* species spiders. (Courtesy of Zach Lemann, Entomologist/Arachnologist, Audubon Nature Institute, New Orleans, LA.)

Therapsids

Tarantulas of the Desert Southwest United States

- Latin: *Dugesia henzi*.
- Venom: ATPase, spermine, hyaluronidase.
- Diagnosis: Rarely bites, local histamine response, barbed urticating hairs fired from abdomen — can lodge in cornea (causing *ophthalmia nodosa*) or even be inhaled (causing asthmatic tracheobronchitis).
- Antidote: None specific.
- Treatment: H₁- and H₂-blockers, adhesive removal of urticating hairs.

Pet Tarantulas

Australian Funnel Web Spiders

- Description: Large (3–5 cm) Australian ground-burrowing or tree-dwelling black spiders with the world's most potent neurotoxin, atraxotoxin (males more venomous than females).
- Latin: *Atrax* (ground dwelling spp.) and *Hadronyche* (tree dwelling spp.).



Figure 16.12 Sydney Funnel Web Spider (*Atrax robustus*), Southeastern Australia. The Sydney funnel web spider (*Atrax robustus*) is considered among the world's most venomous spiders. Its venom contains the potent neurotoxin, atraxotoxin, which can cause the initial massive release of adrenergic and cholinergic neurotransmitters (Stage I), followed by cardiorespiratory depression and death (Stage II). An effective antivenom is available in Australia. (With permission from Mebs D, *Venomous and Poisonous Animals*, CRC Press, Boca Raton, FL, page 193, figure 3.21.)

- Venom: Massive release of acetylcholine (Ach), norepinephrine (NE), and epinephrine (EPI).
- Diagnosis:
 - Stage I: Piloerection, fasciculations, adrenergic tachycardia and hypertension, and cholinergic crisis (SLUDE — salivation, lacrimation, urination, defecation, emesis) within 5 minutes;
 - Stage II: Decreased blood pressure, respiratory depression, pulmonary edema, metabolic acidosis, death, especially in children <4 years.
- Antidote: Specific Australian antivenom, 2 amps every 5 minutes.
- Treatment: Atropine, vasodilators, muscle relaxants, mechanical ventilation.

Scorpion

Bark Scorpion

- Latin: *Centruroides sculpturatus*.
- Venom: Enzymatic complex containing acetylcholinesterase, serotonin, hyaluronidase, phospholipases, and Na-channel-opening neurotoxins that cause massive autonomic discharge with both adrenergic (tachycardia and hypertension) and cholinergic (SLUDE syndrome) manifestations.
- Diagnosis: Grade I — pain, positive tap test (tapping over suspected bite site elicits pain); Grade II — spreading paresthesias and numbness; Grade III — restless shakes, chorea, cranial nerve (CN) palsies, dysarthria; Grade IV — CNS and neuromuscular dysfunction.
- Antidote: Goat-derived IgG antivenom, available in Arizona only.
- Treatment: Sympathetic and cholinergic blockers, Ca gluconate, consider ASA and quinine.

Tick Paralysis

Ixodids and Argasids

- Latin: *Ixodes scapularis*, *Dermacentor andersoni*, *Dermacentor variabilis*, *Amblyomma americanum*, and *Amblyomma maculatum*.
- Venom: Salivary gland bulbospinal neurotoxin.
- Diagnosis: Diarrhea, lower extremity weakness, then ascending paralysis, especially in long-haired girls, mimics Guillain-Barre syndrome (GBS).

TABLE 16.1 Hymenoptera: Unique Venoms

Apid (Bees)	Vespids (Wasps)	Promicids (Fire Ants)
Unique components: Alegern C, apamin, mellitin, minimine	Unique components: Antigen 5, kinin	Unique components: Glucosaminidase, peperindines
Hyaluronidase	Hyaluronidase	Hyaluronidase
Phospholipases	Phospholipases	Phospholipases
Acid phosphatase	Acid phosphatase	
Mast cell degranulation peptide	Mast cell degranulation peptide	



Figure 16.13 North American Bark Scorpion (*Centruroides exilicauda*). A North American Bark Scorpion (*Centruroides exilicauda*, formerly *C. sculpturatus*) devouring a venomous centipede, *Etmostigmus* sp., U.S. desert Southwest. (Courtesy of Dino Ferri, Herpetologist and Assistant Curator of Reptiles and Amphibians, Audubon Nature Institute, New Orleans, LA.)

- Antidote: None.
- Treatment: Remove tick *in toto*, especially mouthparts.

Hymenoptera Species

Apids (Bees)

Honeybee, Bumble Bee, Carpenter Bee

- Latin: *Apis mellifera*, *Bombus* species, *Xylocopa* species.
- Venom: Phospholipase A₂ (12%), hyaluronidase, mellitin (main toxin — 50–60%), apamin, acid phosphatase, allergen C, mast cell degranulating peptide.
- Diagnosis: Local pain — edema, systemic — gastrointestinal symptoms, fever, headache, syncope, seizures, respiratory failure. Anaphylaxis — urticaria, bronchospasm, throat and chest tightness, stridor, cardiovascular collapse and cardiorespiratory arrest.
- Antidote: None, prophylactic desensitization with venoms from apids and vespids.
- Treatment: Scrape out stingers, subcutaneous epinephrine, support airway and circulation.



Figure 16.14 Yellowjacket Queen (*Vespula muculiforma*). Yellowjacket wasps (*Vespula muculiforma*) may sting repeatedly, unlike honeybees, and have complex venoms that can induce anaphylaxis. (Courtesy of Dino Ferri, Herpetologist and Assistant Curator of Reptiles and Amphibians, Audubon Nature Institute, New Orleans, LA.)

Vespids (Wasps)

Paper Wasp, Gold Wasp, Yellow Jacket, White-Faced Hornet

- Latin: Vespids.
- Venom: Kinins, antigen 5, phospholipases, hyaluronidase, mast cell degranulating peptide.
- Diagnosis: Same as apids, consider desensitization.
- Treatment: Scrape out stingers, prepare for anaphylaxis.

Formicids

Southern Fire Ants

- Latin: *Solenopsis* species.
- Venom: Substituted piperidines phospholipase, hyaluronidase, glucosaminidase.
- Diagnosis: Initial red wheals, becoming clear vesicles within hours, then pustules by 12 hours, umbilicate by 24 hours, anaphylaxis possible.
- Antidote: None.

- Treatment: Salt/vinegar wash, topical antihistamines, cold, topical lidocaine, oral H₁-blockers.

Lepidoptera Species

Caterpillars

Nettling Caterpillars

- Nettling caterpillars = browntail moth, Io moth, buck moth, saddleback moth, and puss moth (*Megalopyge opercularis*) caterpillars.
- Venoms: Urticarial toxins in hairs, spines, and hemolymph.
- Diagnosis: Painful sting, white-red papules lead to adenopathy, muscle cramps, seizures, shock possible.
- Antidote: None.
- Treatment: Adhesive removal of spines, consider IV calcium gluconate for muscle cramping, topical corticosteroids.



Figure 16.15 Puss Moth Caterpillar (*Megalopyge opercularis*). The puss moth caterpillar, *Megalopyge opercularis*, is covered with light brown hairs that hide breakaway venomous spines or spicules. (Courtesy of Dino Ferri, Herpetologist and Assistant Curator of Reptiles and Amphibians, Audubon Nature Institute, New Orleans, LA.)

Miscellaneous

Blister Beetles

Blister Beetle (Eastern United States) and Spanish Fly (Europe)

- Latin: *Cantharis vesicatoria* (Europe), *Tegrodera aloga* (United States).
- Venom: Cantharidin, an irritating skin and mucosal vesicant.
- Diagnosis: Blistering, vesicular dermatitis, stomatitis, cystitis, hematuria, priapism, vaginal bleeding, spontaneous abortion.
- Antidote: None.
- Treatment: Supportive.

Centipedes

Centipedes

- Latin: *Chilopoda* species, all centipedes are venomous, but do not bite.
- Venom: Undefined venom; venom delivery apparatus — one pair of specialized poison claws on front feet just behind head.
- Diagnosis: Painful sting from specialized poison claws.
- Antidote: None specific.
- Treatment: Supportive.

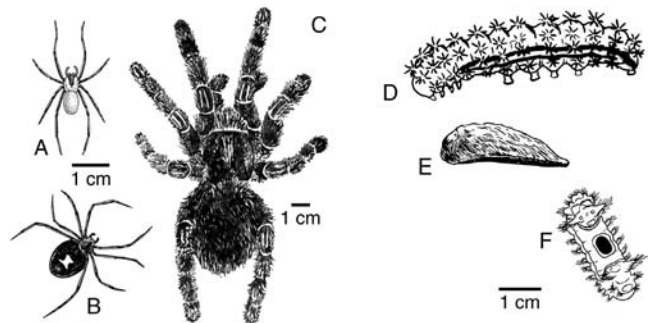


Figure 16.16 A Comparative Study of the Sizes of Venomous Spiders and Caterpillars. Caption: A Brown Recluse (*Loxosceles reclusa*) Female, Dorsal View, Leg Span 1-2 cm. B Black Widow (*Latrodectus mactans*) Female, Ventral View, Leg Span 3-4 cm. C American Southwestern Desert Tarantula (*Aphonopelma hentzi*) Female, Dorsal View, Leg Span 18-24 cm. D Io Moth Caterpillar (*Automeris io*), Lateral View, Length 5-6 cm. E Puss Moth Caterpillar (*Megalopyge opercularis*), Lateral View, Length 2.5-3.5 cm. F Saddleback Caterpillar (*Sibene stimulea*), Lateral View, Length 2-2.5 cm.

Marine Envenomings

Chapter Outline

Taxonomy

Epidemiology

Toxic coelenterates (invertebrates)

Echinoderms

Cnidarians

Mollusks

Toxic vertebrates

Chondrichthyes — stingrays

Scorpaenidae — scorpaenid bony fish

Trachinidae — weeverfish

Reptilia — sea snakes

Taxonomy

TABLE 17.1 Coelenterates (Invertebrates)

Phyla	Species
Porifera	Sponges
Cnidaria	Corals, hydroids, anemones, jellyfish
Annelida	Worms
Mollusca	Snails, octopuses
Echinodermata	Starfish, sea urchins, sea cucumbers

TABLE 17.2 Chordates (Vertebrates)

Classes of the Vertebrate Chordates (Phylum Chordata)		Species
Chondrichthyes		Stingrays and sharks
Osteichthyes		Bony fishes
Scorpaenidae		Lionfish, stonefish, scorpionfish, zebrafish
Trachinidae		Weeverfish
Reptilia		Sea snakes and sea kraits
Hydrophiliidae		Sea snakes

Epidemiology

- Coelenterates, especially corals and jellyfish, cause most marine envenomings.
- The Australian box jellyfish (*Chironex fleckeri*) is the most venomous and deadly (case fatality rate [CFR] 20+%) of all toxic marine life.
- The fire coral (*Millepora* spp.) is the most toxic Cnidarian; the blue-ringed octopus (*Hapalochlaena maculosus*) is the most toxic mollusk; and the crown-of-thorns (*Acanthaster planci*) starfish is the most toxic Echinoderm.
- Stingrays cause 1800 painful envenomings per year in the United States.
- The stonefish (*Synanceja horrida*) is the most venomous Scorpaenid bony fish.
- The lionfish (*Pterosis volitans*) is the most common Scorpaenid in home aquariums.
- Marine venoms are very complex mixtures of low- and high-molecular-weight (MW) proteins, including histamine, prostaglandins, serotonin, kinins, indoles, and many other vasoactive compounds. Most venoms are heat labile and can be inactivated by warm-water immersion.

Toxic Coelenterates (Invertebrates)

Echinoderms

Starfish

- Common name: Crown-of-thorns.
- Latin: *Acanthaster planci*.
- Venom: Toxic saponins with hemolytic, anticoagulant, histaminergic, and neurotoxic properties
- Antidote: None.
- Diagnosis: Puncture wounds, pain, surrounding erythema, nausea, vomiting, parasthesias muscular paralysis, syncope, ataxia.
- Treatment: Hot water immersion (110–115°F) to inactivate heat-labile toxins, tetanus prophylaxis, analgesics.

Sea Urchins

- Common name: Long-spined sea urchin; some species communicate with a venom sac. Venom may also be delivered via triple-fanged jaws called pedicellariae.
- Latin: *Diadema antillarum*.
- Venom: Hemolysins, proteases, serotonin, and steroid glycosides.
- Antidote: None.
- Diagnosis: Edema, erythema, nausea, vomiting, syncope; potential respiratory paralysis, paresthesias and possibly ataxia; and later foreign body (FB) granuloma and sterile nodule formation.
- Treatment: Hot soaks to inactivate heat-labile toxins, tetanus prophylaxis, remove radiopaque spines (especially those embedded in or near joint spaces).

Cnidarians

Corals

- Common name: Fire coral.

- Latin: *Millepora* spp.
- Venom: Histaminergic kinins.
- Antidote: None.
- Diagnosis: Burning/stinging, pruritus, regional urticaria, prolonged wound healing, eventual scarring.
- Treatment: Seawater irrigation, vinegar (acetic acid) soak, papain containing meat tenderizer, skin shave, antihistamines, steroids, tetanus prophylaxis.

Jellyfish

- Common name: Box jellyfish (sea wasp).
- Latin: *Chironex fleckeri*.
- Venom: Myospastic, neurotoxic.
- Antidote: Sheep-derived antivenin (Australia).
- Diagnosis: Immediate linear wheals and blisters (tentacle tracks); then myospasm, respiratory paralysis, hypotension, cardiac arrest.
- Treatment: CPR, antivenin, tetanus prophylaxis.

Jellyfish

- Common name: Portuguese man-of-war, tentacles trail up to 30 meters.
- Latin: *Physalia physalis*.
- Venom: Neurotoxic.
- Antidote: None.
- Diagnosis: Painful linear papules/welts (tentacle tracks), nausea, vomiting, headache, myalgias, chills, respiratory distress, cardiovascular collapse.
- Treatment: Vinegar soak, papain meat tenderizer, skin shave, tetanus prophylaxis, antihistamines.

Miscellaneous Venomous Hydroids and Jellyfish

- Stinging hydroid: *Aglaophenia* spp.; polyp colonies of feathery, tree-like ferns growing on rocks and dead coral. Local inflammatory reactions on skin contact best managed with topical antihistamines and corticosteroids.
- Sea nettle: *Chrysaora quinquecirrha*; pink jellyfish with complex venom of esterases, proteases, hyaluronidase. Severe pain, then blistering tentacle tracks may be followed by skin necrosis. Topical baking soda paste can inactivate venom.
- Mauve stinger: *Pelagia noctiluca* yellow-to-luminescent pink jellyfish; contact causes initial blisters that heal slowly with hyperpigmentation. Systemic toxicity with weakness, headache, nausea, vomiting possible. Topical-like anesthetics more effective for pain than topical antihistamines and corticosteroids.

Larval Jellyfish

- Common name: Sea lice — larval jellyfish.
- Latin: *Linuche unguiculata*.
- Venom: Histamine, kinins.
- Antidote: None.
- Diagnosis: Sea bather's eruption-blisters and hives oriented in a bathing suit distribution, especially under waistbands and straps, with nausea, vomiting, headache common co-morbidities.
- Treatment: Seawater wash, vinegar soak, topical–systemic antihistamines and steroids.

Mollusks

Cone Shells

- Name: Cone shells.
- Latin: *Conus* spp.
- Venom: Conotoxins are neurotoxic venoms that inactivate Na and Ca channels and are injected by a venom tooth on the tip of the cone shells proboscis.
- Antidote: None.

- Diagnosis: Burning, numbness, ischemia, local–distal paresthesias, dysphagia, diplopia; cardiovascular collapse and death possible.
- Treatment: Seawater wash, vinegar soak, topical–systemic steroids and antihistamines.

Octopuses

- Common name: Blue-ringed octopus.
- Latin: *Hapalochlaena maculosus*.
- Venom: Parrot-like beak, two venom-glands, neurotoxic venoms (maculotoxin, cephalotoxin), tetrodotoxin (as in puffer fish and Oregon rough-skinned newt).
- Antidote: None.
- Diagnosis: Burning- numbness, ischemia, paresthesia, aphonia, dysphagia, diplopia, cardiovascular collapse, respiratory failure, coma, death.
- Treatment: Inotropic support, ventilatory support, hot water soak, tetanus prophylaxis.



Figure 17.1 Blue-ringed octopus (*Hapalochlaena maculosus*). The blue-ringed octopus (*Hapalochlaena maculosus*) can inflict a painful bite and inject a tetrodotoxin-containing, paralyzing venom. (With permission from Dietrich Mebs, *Venomous and Poisonous Animals*, CRC Press, Boca Raton, FL, page 72, Figure 2.34.)



Figure 17.2 Masked pufferfish, *Arothron diadema*, Red Sea. The meat of the pufferfish is often consumed raw as “fugu” fish in Japan. The pufferfish and marine sunfish contain high concentrations of paralyzing tetrodotoxin in the skin, liver, bile, ovaries, and roe, and must be filleted precisely in order to be eaten raw or cooked without risk of tetrodotoxin poisoning. (With permission from Dietrich Mebs, *Venomous and Poisonous Animals*, CRC Press, Boca Raton, FL, page 139, Figure 2.91.)

Toxic Vertebrates

Chondrichthyes — Stingrays

- Common name: Southern stingray.
- Latin: *Dasyatis americana*.
- Venom: Serotonin, 5'-nucleotidase, and phosphodiesterase-venom injected by tail barb into deep, jagged lacerations, usually of the leg or foot, and caused by long, serrated spines on the dorsum of the tail.
- Antidote: None.
- Diagnosis: Intensifying burning pain often in cyanotic deep wounds, muscle cramping, weakness, tremor, syncope, hypotension, cardiovascular collapse, seizures, paralysis, secondary marine *Vibrio* infections common — *ecthyma gangrenosa* (*V. vulnificus*) and osteomyelitis.
- Treatment: Hot water immersion to inactivate heat-labile toxins, third-generation cephalosporin, antibiotic prophylaxis, tetanus prophylaxis, debridement, analgesics.

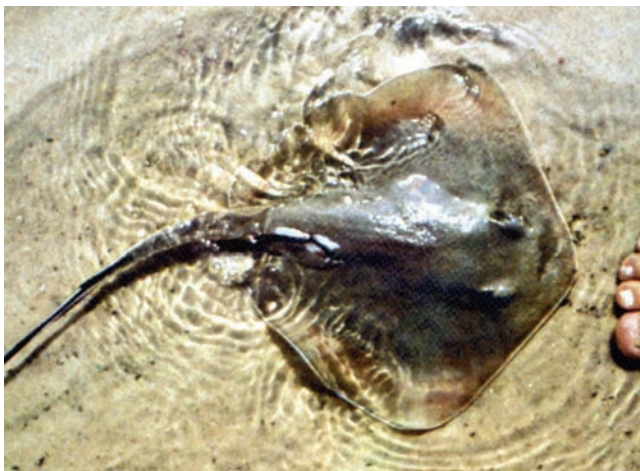


Figure 17.3 Southern stingray (*Dasyatis americana*)
Injuries: Diagnosis and Treatment. Southern stingrays (*Dasyatis americana*) are commonly found in shallow waters off the U.S. Atlantic and Gulf of Mexico coasts and can inflict serious penetrating injuries with sharp spines on their long, whip-like tails.



Figure 17.4 Southern stingray (*Dasyatis americana*).
Southern stingray (*Dasyatis americana*)-inflicted human injuries usually occur on the feet and shins when the stingrays are stepped upon in shallow water and whip their barbed tails over their bodies. (Courtesy of Charles P. Sea, Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, Information Bulletin #12, 1980, "Toxic Fish and Mollusks.")

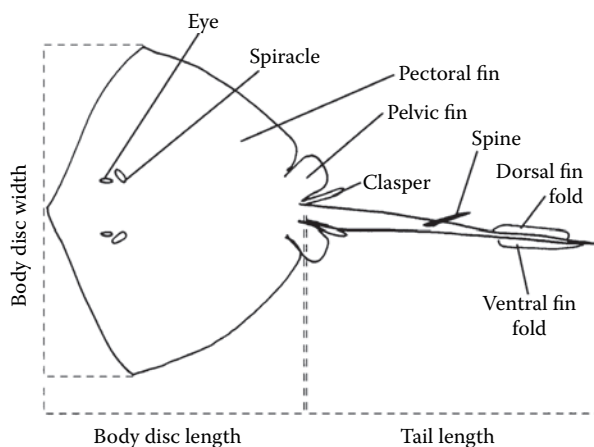


Figure 17.5 Barbed tail spine, southern stingray (*Dasyatis americana*). The hollow barbed spine on the dorsal aspect of the stingray's tail can cause jagged lacerations and inject a heat-labile toxin. (Courtesy of Charles P. Sea, Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, Information Bulletin #12, 1980, "Toxic Fish and Mollusks.")

Scorpaenids — Lionfish

- Common name: Lionfish.
- Latin: *Pterosis volitans*.
- Venom: PGF₂α, PGE₂, thromboxane B₂ (TXB₂) injected by long, curved dorsal spines with separate venom glands.
- Antidote: Scorpaenid polyvalent antivenin (available CDC and major aquariums), reserve for stonefish envenoming.
- Diagnosis: Local severe pain/edema.
- Treatment: Hot water soak, digital block, analgesics, tetanus prophylaxis.



Figure 17.6 Lionfish (*Pterosis volitans*). The lionfish (*Pterosis volitans*) has dorsal fins tipped with sharp spines attached to separate venom glands, which can inflict painful envenoming injuries in divers and saltwater aquaria enthusiasts. A polyvalent Scorpaenid antivenom is available for the management of moderate to severe envenomings caused by lionfish, scorpionfish, and stonefish. (Courtesy of Charles P. Sea, Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, Information Bulletin #12, 1980, "Toxic Fish and Mollusks.")

Scorpaenids — Stonefish

- Common name: Stonefish.
- Latin: *Synanceja horrida*.
- Venom: Myotoxic heat-labile, high-MW proteins injected through sharp spines on dorsal pectoral, and anal fins.
- Antidote: Contact major aquariums.
- Diagnosis: Intensifying local pain, erythema, ecchymoses, induration, hyperesthesia/dysesthesia, nausea, vomiting, dyspnea, diaphoresis, later lymphadenopathy, syncope, hypotension, dysrhythmias.
- Treatment: Hot water immersion (110–115°F), digital block with 0.25% bupivacaine plain, antivenin not universally available — contact CDC and local major aquariums; oral analgesics — NSAIDs + opioids, parenteral opioids often required, drain and unroof blisters filled with venom.



Figure 17.7 Stonefish (*Synanceja* spp.). Stonefish are flattened dorsoventrally, lie camouflaged by sand on the ocean floor, and can inflict painful envenoming injuries with dorsal spines when stepped on by swimmers or divers. (Courtesy of Charles P. Sea, Department of Emergency Medicine, Ochsner Clinic Foundation Hospital, New Orleans, LA. Original Source: U.S. Government Document, Information Bulletin #12, 1980, "Toxic Fish and Mollusks.")

Trachinidae — Weeverfish

- Common name: Weeverfish — small bottom-feeders that burrow into muddy/sandy-bottomed bays of eastern Atlantic, with sharp dorsal and single opercular spines surrounded by venom-containing glandular tissue that will penetrate thick boots.
- Latin: *Trachinus* spp.
- Venom: Ichthyoacanthotoxin composed of high-MW proteins, serotonin, epinephrine, norepinephrine, histamine.
- Antidote: None.
- Diagnosis: Pain, edema, headache, fever, chills, nausea, vomiting, diaphoresis, hypotension, sei-

zures, dysrhythmias, respiratory paralysis. Initial local edema may be followed by induration involving entire extremity and may persist for months.

- Treatment: Analgesics, digital block, tetanus prophylaxis, supportive care.

Reptilia — Sea Snakes

- Common name: Sea snakes and sea kraits.
- Latin: *Aipysurus laevis*, *Astrotia stokesii*, *Enhydra schistosa*, *Hydrophis ornatus*, *H. cyanocinctus*, *Lapemis hardwickii*, and others.
- Venom: Neurotoxin alters Na/Cl permeability, but has no effect on Na-K ATPase pump — also hemolytic and myotoxic (olive sea snake).
- Antidote: Equine-derived bivalent antivenin used for all envenomings.
- Diagnosis: No local reaction, peripheral and cranial nerve (CN) neuropathies within 3–6 hours, paralysis, respiratory failure, myonecrosis and myoglobinuria (esp. olive sea snake), renal failure.
- Treatment: Supportive, antivenin, analgesics, tetanus prophylaxis.

Arthropod Vectors of Human Infectious Diseases

Chapter Outline

Mosquitoes

- Mosquitoes (Culicidae)
- Stages
- Control and prevention

Flies

- Blackflies (Simuliidae)
- Sandflies (Phlebotominae)
- Biting midges (Ceratopogonidae)
- Deerflies and Horseflies (Tabanidae)
- Tsetse flies (Glossinidae)
- Domestic houseflies (Muscidae)

Myiasis-causing flies

- Obligatory myiasis
- Facultative myiasis

Fleas, lice, true bugs, ticks, and mites

- Fleas
- True bugs
- Ticks
- Mites

Conclusions

Mosquitoes

Mosquitoes (Culicidae)

Anophelines (Anophelinae)

- Adults: Only females feed after mating to obtain nutrient blood meals for their eggs; rest at acute angle to feed; digest blood meal over 3 days to 2 weeks; lifespan 1–4 weeks; infective for life.
- Diseases: Human (4 types) and animal malaria, filariasis (*Wuchereria bancrofti*, *Brugia malayi*, *Brugia timori*), zoonotic arbovirus (O’Nyong-nyong — “joint-breaker” fever).
- Mechanism: PM-biting, anthropophagic (bites man) vs. zoophagic (bites animals), endophagic (feeds indoors) vs. exophagic (feeds outdoors), endophilic (lives indoors) vs. exophilic (lives outdoors); mosquito must ingest gametocytes to start sexual cycle — infective sporozoites stored in mosquito’s salivary glands injected on biting.

Culicines (Culicinae)

- Adults: Same feeding behaviors and lifespan as anophelines; rest parallel and not at an angle to host to feed.
- Diseases: *Culex-Wuchereria bancrofti*, *Brugia malayi*; *Aedes*-yellow fever and dengue; both zoonotic arboviruses (Ross River — Australia, Chikungunya — Africa, Asia; Sindbis — Africa, Asia; West Nile — Africa, Asia, Americas, Middle East); encephalitis viruses (Japanese encephalitis, Japan, Asia; Eastern/Western Venezuela–Americas) equine encephalitis.
- Mechanism: Day-biting, anthropophagic and zoophagic, exophagic and endophilic; no malaria transmission, same microfilaria and viral transmission.

Stages

Anophelines

- Adults: Females have nonplumose antennae, palps as long as proboscis, black and white block-like wing scales; feed at angle to host.
- Eggs: Always laid singly with floats (“little canoes”).
- Larvae: No siphon, rest parallel to water surface.
- Pupae: Breathing trumpets short and broad apically (like “Shrek”), hairy spines on segments 2–7.

Culicines

- Adults: Females have nonplumose antennae too, palps much shorter than proboscis, wing veins do not have block-like scales; feed parallel (horizontal) to host.
- Eggs: Laid in rafts or singly with no floats (“life rafts”).
- Larvae: Always have siphons, rest at 45° angle to water surface.
- Pupae: Trumpets short or long, but not broad apically, non-“Shrek”-like, no spines on segments 2–7.

Control and Prevention

- Hierarchy of vector control: Genetic control > physical control > biological control > chemical control > personal protection.
- Genetic control: Complex and expensive, #1 release of infertile and impotent males (hybrids, irradiated, or chemosterilized males) > #2 lethal genomic reengineering (U.S. Naval Researchers and U.S. Army Researchers).
- Physical control: Drainage > landfills > habitat changes = decreased water flow, marsh impoundment to create deep ponds and lakes.
- Chemical control: Oil spraying > insecticides: pyrethroids (deltamethrin, permethrin) >

biodegrading organophosphates (malathion, fenitrothion, chlorpyrifos, pirimiphos, temephos) and carbamates (aldicarb, bendiocarb, propoxur) > bioaccumulating organochlorines: DDT, lindane.

- Personal protection: Pyrethroid-impregnated door and window blinds, coils, mats, nets, screens > clothing > body repellants (diethyltoluamide [DEET]) > dimethylphthalate [DIMP].

Flies

Blackflies (Simuliidae)

- Family: Simuliidae.
- Genus: *Simulium* blackflies or buffalo-flies.
- Adult: Tiny black flies with buffalo-humped thorax, hairless wings, and 3–4-week lifespan.
- Disease: African and Latin American River Blindness (*Onchocerca volvulus*), Southern African filariasis (*Mansonella ozzardi*).
- Mechanism: Daytime-biting females stretch skin with toothed labrum, then use their raspy maxilla and mandible to chew into fine capillaries, creating a blood pool filled with host's circulating microfilaria to drink from.
- Eggs: 200–800 laid in sticky masses at water level in fast-flowing rivers and streams.
- Larvae: Sedentary passive filter-feeders anchored by posterior cirri; characteristic gill spots and apical mouthbrushes.
- Pupae: Slipper-shaped brown cocoons anchored to submerged rocks; simultaneous adult emergence (hatch).
- Control: Organophosphate pesticides (temephos) > DDT in flowing streams, biological control (*Bacillus thuringiensis*).
- Prevention: Personal protection with DEET > DIMP.

Sandflies (Phlebotaminae)

- Genus: *Phlebotomus* (Old World) and *Lutzomyia* (New World).
- Adults: Tiny black flies covered with hairs, large black eyes, stilt-like legs, hairy wings held erect over body at rest.
- Diseases: Leishmaniasis — cutaneous (*Leishmania tropica* and *L. major*), mucocutaneous espundia (*L. braziliensis* and *panamensis*), diffuse cutaneous (*L. aethiopica* and *L. amazonensis*), visceral-kala-azar (*L. donovani* and *L. chagasi*); Bartonellosis (Carrion's disease); viral sandfly fever (transovarian).
- Mechanism: Nocturnal blood-sucking exophagous females ingest amastigotes to mid-

gut, metacyclic promastigotes regurgitated into host at blood meal.

- Eggs: 30–70 minute ovoid eggs with brick patterns oviposited on moist ground, masonry, or leaf litter.
- Larvae: Four (4) stages of segmented instars, all have dark heads, are bristled with matchstick hairs, and tipped with caudal bristles.
- Pupae: Comma-shaped pupa with larval skin remaining attached caudally with characteristic matchstick hairs and caudal bristles.
- Control: Pyrethroid-impregnated blinds, screens, nets, and clothing.
- Prevention: Personal protection — DEET > DIMP > trimethylpentanediol.

Biting Midges (Ceratopogonidae)

- Family: Ceratopogonidae.
- Genus: *Culicoides*, “no-see-ums.”
- Adults: Only minute females bite, small head, prominent eyes, long non-plumose antennae, two (2) dark depressions or humeral pits on head end of thorax, patterned black and white wings.
- Diseases: Filariasis: Africa — *Mansonella perstans* and *M. streptocerca*; Americas — *Mansonella ozzardi*.
- Mechanism: Females ingest dermal microfilaria with blood meals; microfilaria then invade thoracic wing muscles to develop, migrate to head and proboscis in 10 days, and ultimately rupture out of vector during blood-feeds (non-salivary transmission).
- Eggs: 30–250 banana-shaped eggs per oviposition on wet mud or manure.
- Larvae: Four (4) nematode-like instars with dark conical heads, twelve (12) segments, four (4)-lobed retractable papillae.
- Pupae: Paired two-segment breathing trumpets on head and paired spiny thorns on tail.
- Control: Marsh impoundment; aquatic vegetation and bottomland spraying, organophosphates > organochlorines.

- Prevention: Small-mesh pyrethroid-impregnated screens, DEET > DIMP > trimethylpentanediol (TP).

Deerflies and Horseflies (Tabanidae)

- Family: Tabanidae.
- Genus: *Chrysops* (deerflies) and *Tabanus* (horseflies).
- Adult: Large dark flies with semilunar heads and iridescent compound eyes separated in females by a dichoptic space, short stout antennae, wings rest at roof-like angle over abdomen.
- Disease: Loiasis (*Loa loa*), mechanical transmission of bacterial (anthrax, tularemia) and trypanosomal zoonoses.
- Mechanism: Females inflict often-interrupted and frequent deep, painful bites sucking up dermal microfilaria, which develop in thoracoabdominal fat and then migrate to proboscis for non-salivary transmission on next blood meal.
- Eggs: 100–1000 creamy to dark colored eggs oviposited on undersides of vegetation close to aquatic larval sites.
- Larvae: Creamy to dark-colored, large and cylindrical, pointed at both ends, 11 segments separated by tire-like rings — the middle 4–10 of which have pseudopods; characteristic caudal Graber's sensory organ.
- Pupae: Comma-shaped and brown colored, buries itself into mud and resembles butterfly chrysalis.
- Control: Marsh drainage.
- Prevention: Personal protection.

Tsetse flies (Glossinidae)

- Family: Glossinidae.
- Genus: *Glossina*.
- Adults: Both sexes are daytime biters, especially through dark clothing, large yellow-brown to black with rigid, forward projecting proboscis and characteristic upside-down hatchet wing venation, wings rest over abdomen like scissors.
- Diseases: Human (*Trypanosoma brucei gambiense* — chronic sleeping sickness, *T. brucei rhodesiense* — virulent sleeping sickness) and animal (*T. brucei brucei*) African trypanosomiasis.

- Mechanism: Amastigotes sucked up on blood-feed migrate to paired salivary glands and mature into infective metacyclic trypomastigotes, ready for human/animal transmission on the next blood-meal.
- Eggs: No eggs; direct single-larva larvipositors.
- Larvae: Nourished by paired milk glands, 12 segments with paired black polyneustic lobes used to burrow into 2–5 cm of moist, shady soil on oviposition after 9-day gestation.
- Pupae: Resemble a contracted, barrel-shaped larvae with prominent polyneustic lobes; adult flies emerge from buried pupae.
- Control: OCs (dieldrin, DDT) directed at adults since larvae develop within females and pupae are buried; clearing waterfront vegetation; OP-impregnated blue cloth target screens and conical flytraps.
- Prevention: Avoid dark clothes; personal protection.

Domestic Houseflies (Muscidae)

- Family: Muscidae.
- Genus: *Musca domestica*.
- Adults: Medium-sized, nonmetallic color, four (4) dark thoracic stripes, telescoping proboscis designed for siphoning semisolid fluids, three (3) pairs of legs equipped with glandular hairs secreting sticky substances.
- Diseases: Mechanical vectors of bacterial (*Shigella*, *Salmonella*, cholera, ETEC, *Campylobacter*), protozoan (amebic), and viral infectious diseases.
- Mechanism: Feed on feces then human food, mechanically transmitting, vomiting, or defecating infectious microbes.
- Eggs: 75–120 banana-shaped eggs oviposited on decaying matter and feces.
- Larvae: Creamy white, 11-segment cylindrical maggot with pointed heads, two mouthhooks, and posterior pairs of breathing spiracles.
- Pupae: Dry, brown, barrel-shaped pupae develop in dry soil beneath larval habitats.
- Control: Physical — screens, UV-light traps, toxic baits; environmental — refuse disposal; larvicides — OP spraying garbage cans; adulticides — OPs > pyrethroids.
- Prevention: Sanitary food preparation, food and restaurant service monitoring and inspection.

Stable Fly (Muscidae)

- Family: Muscidae.
- Genus: *Stomoxys calcitrans*.
- Adults: Resemble houseflies, but frequent stables and barns; distinctly unique forward-projecting proboscis.
- Diseases: Same as houseflies.
- Mechanism: Same as houseflies.
- Eggs: 50–200 creamy white eggs oviposited in horse manure.
- Larvae: Cream-colored maggots resembling housefly maggots, but with widely separated posterior spiracular slits.
- Pupae: Brown and barrel-shaped pupae resembling housefly pupae, but with characteristic posterior spiracular slits.
- Control: Remove manure; fly traps; OC > OP spraying of breeding sites in stables, barns, and animal shelters.
- Prevention: Sanitary food preparation and consumption away from barns and stables.

Latrine Fly (Fanniidae)

- Family: Fanniidae.
- Genus: *Fannia*.
- Adults: Smaller than houseflies with three (3) longitudinal stripes on thorax.
- Disease: Same as houseflies.
- Mechanism: Same as houseflies.
- Eggs: 50–100 oviposited on feces.
- Larvae: Uniquely distinctive, not maggot-shaped, flattened dorsoventrally and segmented with spines.
- Pupae: Brown and resembles larvae.
- Control: OC > OP spraying of latrine breeding sites.
- Prevention: Proper latrine design and sanitation; sanitary food preparation and consumption.

Myiasis-Causing Flies

Obligatory Myiasis

- Definition: Fly larvae (maggots) must live and feed on a live human or other animal host for part of their life cycle.
- Examples: *Cordylobia anthropophaga* (tumbu fly), *Cochliomyia hominivorax* (New World screwworm), *Chrysomya bezziana* (Old World screwworm), *Dermatobia hominis* (bot fly), *Wohlfahrtia magnifica*.

Facultative Myiasis

- Definition: Normally free-living fly larvae that preferentially feed on carrion and other decaying matter, and only incidentally attack and feed on sores and wounds of live human and animal hosts.
- Examples: *Calliphora* (bluebottles), *Lucilia* (greenbottles), *Phormia*, *Sarcophaga*.

TABLE 18.1 Myiasis: Family Calliphoridae

Name	Distribution	Adult	Eggs	Larva	Myiasis	Treatment
Tumbu	Africa	Big, brown, 4 abdomen segments	300, diapers, soil + urine	Mouth hooks	Spiraclepoke out	Paraffin seal-off
Floor-maggot	Africa	Same, large segment #2	50, mud hut floors	Night feeder	Not true myiasis	Raise bed, OPs
NW screw	Central America, South America	Big, metallic blue-green, stripes	10–50, sores, EE-orifices	Bury deeply	Painful and deep	Irrigation and removal
OW screw	Africa, Asia	Same, only 2 thorax stripes	150–500, wounds	Same	Same	Same
Greenbottle	Ubiquitous	Metallic green, wings hairless	Carrion, feces	Bury superf.	Clean debris	Debride, OPs
Bluebottle	Ubiquitous	Metallic blue, wings hairy	Same	Same	Same	Same

TABLE 18.2 Myiasis: Sarco and Oestridae

Family	Genus	Distr.	Adult	Eggs	Larva	Myiasis	Treatment
Sarcophagidae	<i>Sarcophaga</i>	W	Big, hairy, patterned abdomen	0	40–60 mags on carrion and feces	Cleaners to subcutaneous GI-myiasis	Debride dead tissues
Sarcophagidae	<i>Wohlfahrtia</i>	W	Big, gray, μ and σ on abdomen	0	120–170, sores, EE, deep pits	Same, to dermis	Same
Oestridae	<i>Dermatophobia-bot fly</i>	LA	Metallic blue/flap head mask	6–30, glued-insect — mosquito	Drop to host skin from insects	To subcutaneous, I&D, surgical “boils with breathe holes”	extract

Fleas, Lice, True Bugs, Ticks, and Mites

Fleas

Siphonaptera

- Family: Siphonaptera.
- Genus: *Xenopsylla cheopsis* (rat flea), *Pulex irritans* (human flea), *Ctenocephalides* (dog and cat fleas).
- Adult: Small oval, compressed laterally; hairy, conspicuous black eyes, three (3) pairs of powerful legs with hindlegs specialized for jumping (specialized protein = elastin).
- Disease: *Yersinia pestis* — sylvatic rodent zoonosis: plague may enter urban areas as infected rats die off; human outbreaks may result and precipitate human bubonic plague and epidemic pneumonic plague; murine typhus — rodent zoonosis (*Rickettsia typhi*) with outbreaks occurring in refugee camps and other situations of overcrowding and poor human hygiene.
- Mechanism: Both sexes infected; plague — *Yersinia* block proventricularis, regurgitated undigested + infected feces; *R. typhi* digested, defecated, and rubbed into wounds and delicate mucosal membranes.
- Eggs: Females lay 3–25 sticky, yellow-white eggs/day in dusty crevices near host dwellings; egg lifespan 1 year.
- Larvae: Hatch in 2–14 days, 2–3 instars, pale brown, 13 segments, conspicuous black head and caudal pairs of anal struts; dwell in dusty

cracks near host, dining on regurgitated blood meals of adult fleas and on host feces.

- Pupae: Develop in sticky, white cocoons, camouflaged with dust and mammal dander; adults emerge in 7–14 days, awakened by vibrations or CO₂ emitted by nearby potential animal hosts.
- Control and prevention: OP-impregnated pet spot-on solutions > flea collars; treat kennels — OPs > pyrethroids > OCs; epidemics — insecticides first, then rodenticides; tuck pants in socks, DEET > DIMP > benzoyl benzonate.

Tunga penetrans

- Family: Siphonaptera.
- Genus: *Tunga penetrans* (chigoe or jigger flea).
- Adults: Smaller than most fleas, hairless, no head combs on compressed thorax.
- Diseases: None; burrow deeply into skin.
- Mechanism: Gravid female burrows deeply into peripheral skin-soles, between toes, under fingernails and toenails, buttocks; swells 1000×.
- Eggs: 150–200 oviposited on mud hut floors from gravid female's genital opening, which remains exteriorized with anus.
- Larvae: Hatch in 3–4 days; pupate in 2 weeks.
- Control: Same chemical control; extract gravid females aseptically.
- Prevention: Wear shoes; do not sit on ground naked.

TABLE 18.3 Lice (Anoplura)

Genus	Adult	Nits	Nymphs	Mechanisms/ Diseases	Control/ Prevention
<i>Pediculus humanis</i> (body louse)	Small, flat, & leathery; segmented, 3 pairs stout legs; toothed tube-like mouth, the haustellum, with salivary stylets. Both sexes suck blood. Repeated salivary injections; Patients feel lousy!	6-9 laid/d & glued to clothes seams; hatch in 7-10 days.	3 instars, resemble small adults, mature in 7-12 days.	<i>Pediculosis corporis</i> and <i>capitis</i> — close contact. Louse-borne typhus (<i>R. prowazeki</i>) — feces rubbed in, lice die; BZ-recrudescence; Trench fever (<i>R. quintana</i>) — infected feces rubbed in, lice live; Relapsing fever (<i>B. recurrentis</i>) — crushed lice release spirochetes-rubbed into abrasions and mucosa.	OP > OC dusting; wash clothes in hot water > 60°C, then iron clothes.
<i>Pediculus capitis</i> (head louse)	Same as body lice, only 10-20 per host.	6-8 nits laid/d, each clinging to single hairs above ears and on neck.	Same as body.	Close contact spread; but no major disease, yet may transmit impetigo.	Remove nits; OC (lindane) shampoos — OCs > dusts > OPs; reg shampoos.
<i>Phthirus pubis</i> (crab-pubic louse)	Smallest lice; broad, squat, crab-like body, large, broad mid & hind legs with claws, slender front legs with thin claws.	150-200 nits cemented to coarse genital & perianal hairs > beard > eyelashes; > 1 nit/hair.	Same as body	<i>Pediculosis pubis</i> (Phthiriasis): STD, fomites = bedding & clothing; potential typhus transmission.	OPs (malathion, carbaryl) > OCs (DDT) lotions; hot-washing of bedding and clothing.

True Bugs

Bedbugs (Cimicidae)

- Family: Cimicidae.
- Genus: *Cimex lectularius* (common bedbug, worldwide) and *Cimex hemipterus* (tropical).
- Adults: Brown, oval, flattened dorsoventrally, wingless — vestigial hemelytra; short, broad heads with retractable proboscis, eight-segment abdomen; male has curved penis and female has a spermatheca or sperm receptacle (“vagina”), known as the organ of Berlese. Adult lifespan: 2–5 years.
- Diseases: Potential transmission of hepatitis B virus; infant iron deficiency in tropics.
- Mechanism: Both sexes reside comfortably in dark bedroom crevices, and between mattresses and box-springs; enjoy pre-dawn nighttime blood-meals; and then return to gregarious communal living at dawn.
- Eggs: 6–10 eggs/week, pearly white with fine and delicate mosaic patterns on shells and slight anterior upturn at opercular ends; cemented between comfortable bedding layers, wallpaper layers, and drywall cracks; hatch within 8–11 days with empty shells remaining as thoughtful calling cards from guests.
- Nymphs: Five (5) nymphal instars enjoy blood-meals on any mammal and mature into adults within 5–8 weeks.
- Control: Recognize infestation; spray or “bomb” floors, walls, and beds (then air) with OPs > pyrethroids > OCs.
- Prevention: Select appropriate nighttime dwellings.

Triatomid Bugs (Triatominae)

- Family: Triatominae; Subfamily: Reduviidae (assassin, cone-nose, kissing, and “stink” bugs).
- Genera: *Triatoma*, *Rhodnius*, and *Panstrongylus* spp.
- Adults: Big 1–2-inch bugs with long snouts and dark eyes; 4-segment antennae; thin, straight, retractable proboscis; triangular thorax, folding wings with contrasting dark (brown-orange) and light (yellow-pink) colors. Powerful flyers.
- Diseases: Chagas disease (*Trypanosoma cruzi*) — a wild-animal zoonosis, especially among armadillos, opossums, squirrels, and rodents.

- Mechanism: Nymph/adults of both sexes feed voraciously and nocturnally for 10–30 min on sleeping human hosts snug in bed up to their eyes/noses; adult females soon defecate infective feces, later rubbed into bite wounds and delicate ocular and nasal mucosa.
- Eggs: 200–300 white-to-pinkish oval eggs with constricted necks just before opercular ends deposited in cracks and crevices in walls, floors, and thatched roofs.
- Nymphs: Emerge after 15–30 days, small and pale, resemble adults, but cannot fly, five (5) instars — all voracious nocturnal blood-feeders that can transmit *Trypanosoma cruzi* — triatomid infection rates in Latin America are 25–40%.
- Control: Interior spraying of residual insecticides — OPs > pyrethroids > OCs. OP-impregnated interior paints.
- Prevention: Plaster or sheetrock interior walls, replace mud-sealed walls with bricks/concrete blocks to eliminate cracks; replace thatched roofs with corrugated metal roofs.

Cockroaches (Blattaria)

- Family: Blattaria.
- Genus: *Periplaneta americana*, *Blatta orientalis*.
- Adult: Large 1–5 cm long, chestnut brown, flattened dorsoventrally, shiny-smooth and tough integument; prominent paired antennae; chewing mouthparts — no stylets — cannot suck blood; three (3) pairs of hairy legs; wings scissor-folded over abdomen, rarely fly; lifespan 2+ years.
- Diseases: Viruses (polio), protozoa (amoebae, *Toxoplasma gondii*), helminths (pinworms), bacteria (*Salmonella/Shigella*, *Staph*, *Klebsiella*).
- Mechanism: Mechanical transmission by regurgitation and excretion of partially digested omnivorous meals (blood, hair, feces, dead insects, etc.) over foods.
- Eggs: Oothecae containing 12–15 eggs deposited in cracks and crevices in warm, dark, and secluded places within homes, empty buildings, and hospitals.
- Nymphs: Hatch within 1–3 months, six (6) instars, cannot fly, wings develop gradually to operational adult wings.
- Control: Domestic spraying (OPs + pyrethroids > OPs [malathion, primiphos, fenthion, diazinon, chlorpyrifos] and carbamates [carbaryl,

propoxur, bendiocarb] > pyrethroids [permethrin, deltamethrin, cypermethrin, lambda-cyhalothrin] > OCs); boric acid tablets/powder; pheromone-impregnated roach traps.

- Prevention: Kitchens and households cleaned of dirty utensils and food spills; pyrethroid and OP-impregnated varnishes and lacquers.

Ticks

- Class: Arachnida; Subclass: Acari.
- Ticks: Worldwide distribution; much larger than mites; toothed hypostome; no claws on palps.
- Soft-bodied ticks (Argasidae): Genus: *Ornithodoros moubata* complex.
- Hard-bodied ticks (Ixodidae): Genera: *Ixodes*, *Dermacentor*, *Amblyomma*.
- Mites: Worldwide distribution; miniscule: 0.45-mm — scabies mites to 1–2 mm for scrub typhus mites.
- Scabies mites (Sarcoptidae): Genus: *Sarcoptes scabiei*.
- Scrub typhus mites (Trombiculidae): *Leptotrombidium*.

Soft Ticks (Argasidae)

- Genus: *Ornithodoros moubata* complex.
- Adult: Oval, flat, wrinkled-leathery integument, ventral mouthparts not visible dorsally except in larvae, four pairs legs with terminal claws; unique paired coxal glands open between base of first 2 paired legs and filter excess sodium and water from blood-meals.
- Diseases: Tick paralysis, tick-borne relapsing fever (*Borrelia duttoni*), Q-fever (*Coxiella burnetii*).
- Mechanism: Both salivary and coxal glands can transmit infectious agents into bite wounds during prolonged blood-meals; transovarial and transstadial transmission common.
- Eggs: Following a blood-meal up to 12 times the body weight, females lay 4–6 batches of

15–100 spherical eggs in cracks, crevices, mud, and debris near host dwellings.

- Larvae: Hatch within 1–3 weeks and resemble adults with three pairs of legs and forward projecting capitellums; blood-feed-transstadial transmission.
- Nymphs: 4–7 instars; all blood-feed.
- Control: Home spray — OPs, carbamates.
- Prevention: Coat tick with volatile antiseptics and then forcep-remove *in toto*; personal protection — pants legs tucked into socks, pyrethroid-impregnated clothing, DEET > DIMP > dibutyl phthalate > dimethyl carbate.

Hard Ticks (Ixodidae)

- Genera: *Ixodes*, *Dermacentor*, *Amblyomma*.
- Adult: Oval, flat, capitulum projects forward, festooned, male scutum larger than female, four (4) pairs of legs with terminal claws; no coxal glands.
- Diseases: Bacterial (Lyme disease, tularemia); rickettsial (Rocky Mountain spotted fever (RMSF), Boutonneuse and Q-fevers, Siberian tick typhus; protozoal (babesiosis, ehrlichiosis); toxic (tick paralysis); arboviral encephalitis.
- Mechanism: All stages exhibit questing behavior and blood-feed on up to three hosts; salivary-transovarial-transstadial transmission.
- Eggs: 1000–8000 small, spherical eggs laid in sticky, gelatinous mass in front and atop female scutum over 10 days, then female dies.
- Larvae: Minute, seed-tick larvae hatch in 10–20 days, and resemble small adults with three (3) pairs legs; quest for hosts (by warmth, CO₂, vibrations); feed once a week, drop off and mature into nymphs.
- Nymphs: One (1) instar, eight-legged.
- Control: Peridomestic spraying; acaricide dips (sheep, cattle) and pet solutions: OPs, carbamates.
- Prevention: Skin inspection, tick removal, pants stuck into socks, DEET > DIMP.

TABLE 18.4 Ixodid-Transmitted IDs

Microbes	Diseases	Agents	Vectors	Distribution
Bacterial	Lyme disease	<i>B. burgdoferi</i>	<i>Ixodes</i>	North America, Europe
	Tularemia	<i>F. tularensis</i>		North America
Rickettsial	RMSF	<i>R. rickettsia</i>	<i>Dermacentor</i>	Russia
Rickettsial	Siberian T Typ	<i>R. sibirica</i>	<i>Dermacentor</i>	Europe, Asia
Rickettsial	Boutonneuse	<i>R. conori</i>	<i>Rhipicephalus</i>	Worldwide
Rickettsial	Q-fever	<i>Cox. burneti</i>	<i>Ixodes</i>	North America, Europe
Protozoal	Babesiosis	<i>Bab. microti</i>	<i>Ixodes</i>	North America
Protozoal	Ehrlichiosis	<i>E. chaffeensis</i>	<i>Ixodes</i>	
Toxic	Tick paralysis	Toxic salivary secretions	<i>Dermacentor</i> , <i>Amblyomma</i>	

TABLE 18.5 Tick-Transmitted Arboviruses

Arboviral Diseases	Tick Vectors	Distribution
Russian spring–summer encephalitis	<i>Dermacentor</i>	North Asia, Russia, China
Colorado tick fever	<i>Dermacentor</i>	North America
Tick-borne encephalitis	<i>I. ricinus</i> , <i>Dermacentor</i>	Northern Europe
Omsk hemorrhagic fever	<i>Ixodes</i> , <i>Dermacentor</i>	Russia
Kyasanur forest disease	<i>Haemaphysalis</i>	India, Southeast Asia
Crimean-Congo hemorrhagic fever	<i>Amblyomma</i> , <i>Dermacentor</i>	Africa, Asia
Powassan encephalitis	<i>Ixodes</i>	North America, Russia

Mites

Scabies Mites (Sarcoptidae)

- Genus: *Sarcoptes scabiei*.
- Adults: Tiny, white, disk-shaped, numerous dorsal pegs; four (4) pairs of short fat legs, mouthparts project anteriorly; smaller males — suckers on the fourth pair of legs.
- Diseases: Scabies (female tunnels — fecal pepper spots, larval moulting pockets, pruritic allergic rash); Norwegian crusted scabies in immunocompromised hosts, often homeless persons.
- Mechanism: Highly contagious on close contact — holding hands, sharing beds and clothing, overcrowding — refugees; females burrow into thin skin on hands, scrotum, buttocks; mating occurs in thin twisting mating tunnels and larvae form moulting pockets in hair follicles.
- Eggs: Females mature — mate in moulting pocket, then tunnel into epidermis, feed on lymph and stratum corneum, lay 1–3 eggs, hatch in 3–5 days.
- Larvae: Six-legged and resemble adults; create a moulting pocket within a hair follicle and mature into nymphs.
- Nymphs: Eight (8) legs; males surface then burrow into moulting pockets to fertilize young females, which then remain in their tunnels to lay eggs.

- Control: Topical 20–25% benzoyl benzoate, liquid sulfur (Mitigal®, Tetmosol®), 0.5% malathion.
- Prevention: Improve personal hygiene, washing and not sharing clothes and bedding.

Scrub Typhus Mites

- Family: Trombiculidae.
- Genera: *Eutrombicula* — red bugs or chiggers (scrub itch); *Leptotrombiculidum* (scrub typhus).
- Adults: Small, red, figure-of-8 shape, velvety hairs, 4 pairs of legs — terminal claws, forward projecting palps and mouthparts.
- Diseases: Scrub-chigger itch, scrub typhus (*Rickettsia tsutsugamushi*).
- Mechanism: Only larvae transmit disease via transovarial transmission, especially in fringe habitats or “mite islands” separating two vegetation zones; larval mites leave eggshells in 5–7 days, feed via hypostomes every 2–10 days on host lymph and skin in warm moist crural, perianal, waist, and ankle areas; anywhere clothing is tight against skin.
- Eggs: Gravid female lays 1–5 spherical eggshells/day in leaf litter in mite islands in damp, well-drained soil; eggshell splits by 1 week,

larvae then emerge to quest and attach to mammalian hosts.

- Larvae: Very small, red-orange, with three (3) pairs of legs terminating in large claws; resemble adults, but less hairy; highly infectious as a result of transovarial transmission and prolonged blood-feeding for 2–10 days.
- Nymphs: Engorged larvae drop of host after 2–10 days, bury in leaf litter, mature in complex life cycle: eggshell, infective pre-larval deutovum,

infective larva, infective protonymph, nymph, infective pre-adult, noninfectious adult.

- Control: Herbicide then insecticide spraying: OPs > pyrethroids > OCs.
- Prevention: Impregnated clothing, DEET.

Conclusions

- Mosquitoes remain the most important vectors of the most unique and virulent infectious diseases, including protozoal (malaria), parasitic (filariasis), and arboviral (dengue, yellow fever, equine encephalides) diseases.
- Flies are often overlooked as mechanical vectors of foodborne bacterial infectious disease outbreaks (*Shigella* and *Salmonella*) and as livestock devastators (screw-worms).
- Fleas and lice are important vectors of highly contagious (fleas-plague) and easily transmissible (murine and louse-borne typhus) infectious diseases, especially in crowded human shelters and refugee camps.
- Ticks are the most versatile insect vectors able to transmit all varieties of microbes (viral, bacterial, protozoal) due to unique combinations of transovarial and transstadial transmission, and prolonged blood-feeding on multiple mammalian hosts.
- The HIV/AIDS epidemic, especially in Africa and Southeast Asia, has created an enlarging population of immunocompromised human hosts at greater risk of developing complicated vector-borne infectious diseases, even relatively innocuous insect-borne diseases, e.g., scabies (Norwegian crusted scabies) and arboviral meningoencephalitis (West Nile virus, Rift Valley fever).

Pesticide Poisoning: Insecticides, Rodenticides, and Herbicides

Chapter Outline

Insecticides

- Organochlorines (OCs)
- Organophosphates (OPs)
- Organophosphate nerve gases
- Neurological complications of organophosphate (OP) poisoning
- Carbamates
- Pyrethrins
- N,N-diethyltoluamide (DEET)

Rodenticides

- Epidemiology
- Toxicology
- Management of unknown rodenticide ingestions
- Toxidrome differential diagnosis

Herbicides

- Paraquat
- Diquat
- Chlorphenoxyacetic acid herbicides

Insecticides

Organochlorines (OCs)

Classes

- DDT: DDT and its analog, methoxychlor; low to moderate toxicity; not biodegradable and bioaccumulating in the environment.
- Lindane (for head lice): Moderate toxicity and in frequent use; consider OC poisoning from excessive lindane absorption in the differential diagnosis of pediatric seizure disorders.
- Cyclodienes: Aldrin, dieldrin, endrin, chlordane, chlordecone (Kepone®), and heptachlor (Mirex®); all highly toxic, some carcinogenic, and still in use illicitly in the United States and licitly in the developing world.
- Toxaphene: Moderate toxicity; infrequent use.

Organochlorines (OCs)

- Representatives: DDT, lindane, cyclodienes.
- Mechanism: Prolonged opening of Na channels.
- Metabolism: Very lipid soluble; preferred absorption pathways include ingestion (gastrointestinal > inhalation (pulmonary) > dermal absorption; all OCs cytochrome P-450 inducers.
- Diagnosis: History, radiopacities on flat and erect abdominal x-rays.
- Antidote: Dextrose and thiamine for seizures.
- Acute: Initially nausea and vomiting; then weakness, paresthesias, tremor, clonus, seizures, fever; seizure activity, respiratory paralysis, respiratory arrest.
- Chronic: Chlordane causes leukemia and thrombotic thrombocytopenic purpura (TTP); chlordecone causes pseudotumor cerebri and male infertility.
- Treatment: Skin decontamination; careful gastric lavage, then AC; seizure control with dextrose, thiamine, benzodiazepines, phenobarbital; cholestyramine to reduce chlordecone enterohepatic circulation. No oil cathartics

— the high lipid solubility of oil cathartics will increase the gastrointestinal absorption of all fat-soluble OC pesticides.

Organophosphates (OPs)

- Representatives: Parathion, malathion, tri-ortho-cresylphosphate (TOCP) (causes Jamaican *ginger-jake* paralysis).
- Symptoms: Cholinergic overstimulation effects = muscarinic (salivation, lacrimation, urination, defecation, gastric, emesis — SLUDGE); nicotinic (neuromuscular junction blockade); and CNS (miosis).
- Mechanism: Prolonged, phosphorylated acetylcholinesterase (AChE) inhibition (aging).
- Pharmacology: All route absorption.
- Antidote: Atropine and 2-PAM.
- Treatment: Decontamination, AC, benzodiazepines for seizures. Confirm normalizing AChE levels post-PAM therapy. Evaluate both plasma and red blood cell (preferred for OP poisoning) AChE levels.

Organophosphate Nerve Gases

Mechanism and Classification

- Mechanism: Long-term AChE inhibition with rapid aging.
- German (G) agents (1936–1945) include:
 - GA: tabun
 - GB: sarin
 - GD: soman
 - GF: CMPF
- British agent: VX.

Prophylaxis and Treatment

- Prophylaxis: (1) Pyridostigmine, a carbamate anti-AChE oxime that temporarily and reversibly inhibits and binds AChE, protecting enzyme

from permanent aging by nerve gas agent; (2) seizure prophylaxis with diazepam.

- Treatment: Neoprene, not latex, gloves for caregivers; immediate skin decontamination; atropine as an antimuscarinic; pralidoxime as an antinicotinic, diazepam for seizures; airway protection and ventilatory support.

Neurological Complications of Organophosphate (OP) Poisoning

OP-Induced Delayed Neuropathy (OPIDN)

- Representatives: OPs only.
- Onset: 1–3 weeks post exposure to OPs.
- Mechanism: “Dying-back” peripheral neuropathy from myelin dissociation, associated with excessive over-accumulation of acetylcholine (ACh) at neuromuscular junctions (NMJ) with overwhelming cholinergic crisis.
- Symptoms: Weakness, glove and stocking paresthesias, muscle cramps, spasticity, ataxia, paralysis, eventual muscle atrophy; irreversible to slowly reversible over 6–15 months.
- Treatment: Supportive.

Intermediate Syndrome (IMS)

- Representatives: Same, OPs.
- Onset: 24–96 hours post cholinergic crisis.
- Mechanism: May result from inadequate oxime treatment, with prolonged nicotinic and CNS ACh stimulation.
- Symptoms: Bulbar, nuchal, and proximal limb weakness due to cranial nerve dysfunction, often with respiratory paralysis; most patients will recover within 12–28 days.
- Treatment: Supportive.

Carbamates

- Representatives: Aldicarb, carbaryl, propoxur.
- Symptoms: Muscarinic (SLUDGE), nicotinic (neuromuscular junction blockade), and CNS (miosis) cholinergic overstimulation effects; but less CNS penetration.
- Mechanism: Short-term carbamoylated AChE inhibition without aging.
- Pharmacology: All route absorption.

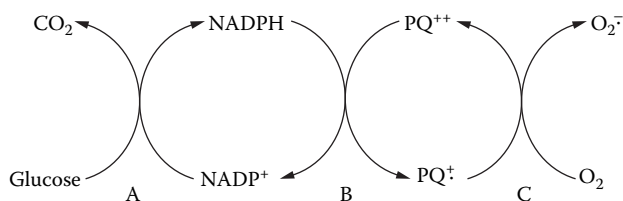


Figure 19.1 The mechanisms of paraquat poisoning. Paraquat (PQ) cations are reduced by lung NADPH to cationic radicals, which then chain-react with alveolar oxygen to form superoxide anionic radicals, which destroy the lung’s alveolar lining cells.

- Antidote: Atropine alone, no oximes because AChE inhibition is reversible.
- Treatment: Decontamination, AC, benzodiazepines for seizures. Confirm normalizing AChE levels post-PAM: plasma and red blood cells AChE levels.

Pyrethrins

- Pyrethrins: Natural extracts from *Chrysanthemum* spp. flowers.
- Pyrethroids: Synthetic pyrethrins:
 - Type I: Permethrin
 - Type II: Deltamethrin
- Mechanism: Inactivation and prolonged opening of Na channels.
- Toxicity: II > I, nausea, vomiting, dizziness, paresthesias, fasciculations, seizures, coma.
- Treatment: Support, atropine, benzodiazepine.
- Least toxic, over-the-counter (OTC) insecticides.

N,N-Diethyltoluamide (DEET)

- Mechanism: “Knock-down” agent causing prolonged opening of Na channels, available concentrations 5–100%, long-acting — 4 to 8 hours.
- Toxicity: Rarely from high absorbed dose = ataxia, seizures, encephalopathy, respiratory failure possible.
- Predisposition: Children, women, pregnant, skin diseases — increases absorption.
- Treatment: Supportive
- Least toxic, over-the-counter (OTC) skin-applied insect repellent.

Rodenticides

Epidemiology

- Prevalence (1990–1995): 17,000 cases.
- Who: 90% children <6 years old.
- Case fatalities: <6 deaths/year.
- Risk factors: Children, elderly, psychotics, exterminators, suicides, homicides, unintentional ingestions of rodenticides stored in empty food containers.

Toxicology

High Toxicity

Thallium

- Physical properties: White, crystalline, odorless, tasteless powder.
- Mechanism: Combines with mitochondrial sulfhydryl groups to interfere with oxidative phosphorylation.
- Onset: Acute gastrointestinal illness, later painful peripheral sensory neuropathy within 2–5 days.
- Symptoms: Nausea, bloody vomitus and diarrhea, ileus; later headache, painful peripheral sensory neuropathy, myalgias, coma, seizures; later alopecia and Mees lines on fingernails > toenails.
- Antidote: Prussian blue (ferric ferrocyanide) to bind thallium.
- Treatment: Lavage and oral activated charcoal (AC).

Sodium Monofluoroacetate

- Physical properties: Same
- Mechanism: Blocks Krebs tricarboxylic acid (TCA) cycle.
- Onset: Delayed 1–2 hours.
- Symptoms: Initial hypotension, nausea, seizures, coma, tachydysrhythmias.
- Antidote: None

- Treatment: Lavage and AC, sorbitol cathartic; glycerol monoacetate = possible antidote?

Strychnine

- Physical properties: Bitter white powder, potential cocaine and heroin adulterant.
- Mechanism: Blocks glycine motor inhibition in spinal cord.
- Onset: 10–20 minutes.
- Symptoms: Sensorium remains intact with twitching, hyperextension, opisthotonos may lead to skeletal fractures, trismus with risus sardonicus.
- Antidote: None.
- Treatment: Immediate lavage and AC, benzodiazepines, barbiturates, muscle relaxants; supportive and quiet room to avoid triggering extensor spasms.

Zinc Phosphide

- Physical properties: Dark, gray powder, smells like rotten fish.
- Mechanism: Releases phosphine gas and zinc on contact with water and gastric acid.
- Onset: Within hours.
- Symptoms: Rotten fish breath, black vomit, tetany from hypocalcemia, seizures, pulmonary edema from inhalation, cardiovascular collapse, acute tubular necrosis (ATN).
- Antidote: None.
- Treatment: Immediate dilution with water, milk, or NaHCO_3 to reduce gastric acidity; then lavage–AC–cathartic; consider proton-pump inhibitor to pharmacologically reduce gastric acidity.

Yellow Phosphorus

- Physical properties: Yellow paste.
- Mechanism: Severe local burns.
- Onset: 1–2 hours.

- Symptoms: Luminescent and smoking vomitus and stool, severe skin and gastrointestinal mucosal burns, cardiovascular collapse, coma, jaundice.
- Antidote: Orogastic lavage with KMnO_4 or H_2O_2 to oxidize phosphorus to harmless phosphates.
- Treatment: AC, cathartic, IV dextrose.

Arsenic

- Physical properties: White crystalline powder.
- Mechanism: Combines with sulfhydryl groups like thallium.
- Onset: 1 hour, death 24 hours.
- Symptoms: Garlic breath, acute dysphagia, muscle cramps, seizures, vomiting and bloody diarrhea, then cardiovascular collapse.
- Antidote: BAL IM > succimer orally > d-penicillamine orally for chelation.
- Treatment: Immediate lavage, AC, cathartic.

Phosphorus: Red vs. Yellow Phosphorus

Red Phosphorus

- Use: “Safety” matches; replaced yellow phosphorus on matches.
- Toxicity: Nonvolatile and insoluble; harmless when ingested.
- Treatment: None indicated.

Yellow Phosphorus

- Use: Rodenticides and explosives.
- Toxicity: Volatile and more soluble.
- Skin: 2nd–3rd degree burns.
- Gastrointestinal: “Smoking” and luminescent vomitus and stools.
- Cardiovascular: Direct myocardial depression.
- Treatment: Emesis — orogastric lavage with 0.1% KMnO_4 or 2% H_2O_2 to oxidize phosphorus to harmless phosphates, then AC and sorbitol (no magnesium containing or oil cathartics).

Barium Carbonate

- Physical properties: Shiny, lumpy water-soluble yellowish powder; unlike insoluble, harmless

barium sulfate frequently used as x-ray contrast media.

- Mechanism: Rapid reduction in extracellular potassium with corresponding increase in intracellular K^+ causes initial skeletal and cardiac muscle hyperpolarization with myospasticity and clonus followed by weakness, respiratory muscle paralysis, and ventricular tachyarrhythmias.
- Onset: 1–8 hours.
- Symptoms: Nausea, vomiting, diarrhea, abdominal pain, hypokalemic paralysis, dysrhythmias — cardiovascular collapse
- Antidote: None.
- Treatment: Lavage with sodium thiosulfate to form harmless, insoluble barium sulfate, replace K^+ losses.

Vacor (pyridyl-nitrophenyl urea, PNU)

- Physical properties: Smells like peanuts, looks like cornmeal, withdrawn in the 1980s.
- Mechanism: Stops NAD production and targets and destroys pancreatic β islet cells, like alloxan and streptozotocin, the experimental diabetes toxins.
- Onset: 4–48 hours.
- Symptoms: Hyperglycemia, diabetic ketoacidosis with autonomic (low blood pressure) and peripheral neuropathy, orthostatic hypotension, gastrointestinal perforation.
- Antidote: Niacinamide (nicotinamide), 500 mg IM or IV, then 200 mg every 4 hours, repeat after 48 hours, preferred over niacin (nicotinic acid).
- Treatment: Early emesis, then lavage, AC and cathartic; insulin and glucose.

Barium: Soluble vs. Insoluble

Insoluble Barium

- Representative: Barium sulfate.
- Use: Oral and rectal radiographic contrast agent.
- Toxicity: Insoluble and harmless when ingested.
- Treatment: None indicated.

Soluble Barium

- Representatives: Barium acetate, barium carbonate, barium chloride, barium hydroxide, barium nitrate, barium sulfide.
- Use: Rodenticides (barium carbonate).
- Toxicity: Causes profound reduction in extracellular K^+ due to increasing membrane permeability to K^+ , driving extracellular K^+ into skeletal and cardiac muscle cells.
- Cardiopulmonary and renal: Low K^+ = arrhythmias, chronic heart failure; hypokalemic respiratory paralysis; acute renal failure.
- Treatment: Oral gastric lavage with sodium thiosulfate to convert soluble barium compounds to harmless, insoluble barium sulfate ($BaSO_4$).

Moderate Toxicity

alpha-Naphthylthiourea (ANTU)

- Physical properties: Odorless, blue-gray powder.
- Mechanism: Targets and destroys rodent pulmonary capillaries by increasing capillary permeability, causing pulmonary edema and pleural effusions.
- Symptoms: Dyspnea, cyanosis, pulmonary edema, pleural effusions.
- Antidote: None.
- Treatment: Immediate emesis, lavage, AC, cathartic.

Cholecalciferol (Vitamin D_3)

- Physical properties: Vitamin D_3 pellets/pills.
- Mechanism: Rapidly mobilizes calcium from bones to cause hypercalcemia.
- Onset: Hours to days.
- Symptoms: High levels of Ca — weakness, metastatic calcifications throughout cardiovascular system and kidneys, osteomalacia.
- Antidote: None.
- Treatment: Emesis or lavage, AC, sorbitol, fluids — replace K and Mg; furosemide, prednisone, and calcitonin to reduce high calcium levels.

Low Toxicity

Red Squill

- Physical properties: Cardiac glycosides, scillaren A and B, extracted from the sea onion plant.
- Mechanism: Digitalis toxicity.
- Onset: 30 minutes to 6 hours.
- Symptoms: Digitalis toxicity = nausea, vomiting, cramping abdominal pain, ventricular dysrhythmias, atrioventricular (AV) blocks.
- Antidote: Digoxin-specific fragment antibodies (Fabs).
- Treatment: Lavage and AC, lidocaine, atropine, pacemaker.

Norbormide

- Physical properties: Resembles yellow cornmeal.
- Mechanism: Specific rodent irreversible smooth muscle vasoconstrictor.
- Symptoms: Hypothermia and hypotension.
- Antidote: None.
- Treatment: Emesis or lavage and AC with cathartic.

Bromethalin

- Physical properties: Green pellets.
- Mechanism: Uncouples oxidative phosphorylation in mitochondria, reduces ATP production.
- Onset: Immediate.
- Symptoms: Muscle tremors, myoclonic jerks, severe flexor spasms, seizures.
- Antidote: None.
- Treatment: Supportive.

Anticoagulants

- Physical properties: Short-acting warfarins and long-acting hydroxycoumarins (or superwarfarins).
- Mechanism: Vitamin K antagonism, clotting factor interference.
- Onset: 12–48 hours to longer.
- Symptoms: Bleeding and increased prolonged prothombin time.
- Antidote: Vitamin K.

- Treatment: Vitamin K, fresh frozen plasma (FFP), whole blood (WB), gastrointestinal decontamination with AC.

Management of Unknown Rodenticide Ingestions

Immediate Supportive Care

- Assure ABCs.
- Identify type and quantity of rodenticide ingested.
- Identify toxidrome by careful physical examination.
- Order precise labs: CBC, PT, glucose, K, Mg, Ca, HCO₃, liver function tests (LFTs), BUN, creatinine.

Toxidrome Differential Diagnosis

Steps to Take

1. Careful physical examination for unusual findings (e.g., alopecia from thallium).
2. Smell breath; smell and examine vomit and stool.

3. Look for a few salient lab abnormalities within an almost completely normal lab panel otherwise.
4. Immediately assess clotting status, because anticoagulants are the most commonly ingested rodenticides.

Poisons to Consider

1. Painful paresthesias, then alopecia = thallium.
2. Irritability, then seizures = sodium monofluoroacetate (SMFA).
3. Opisthotonos and awake, then seizures = strychnine.
4. Rotten fish breath, black vomitus, then cardiovascular collapse = zinc phosphide.
5. Smoking vomit and stool = yellow phosphorus.
6. Dysphagia with bloody vomit and diarrhea = arsenic.
7. Diabetic ketoacidosis, peanut breath, and diabetic neuropathy = Vacor (pyridyl-nitrophenylurea).
8. Dyspnea, then pulmonary edema = alpha-naphthylthiourea (ANTU).
9. Hypercalcemia and its associated findings = cholecalciferol.
10. Easy bruising and bleeding = warfarins (coumarins) and superwarfarins.

Herbicides

Paraquat

- Paraquat physical properties: Water-soluble, dark brown liquid, looks like Coca-Cola®; rapid gastrointestinal absorption, little skin and lung absorption; common suicide agent in India and Southeast Asia.
- Mechanism: Very corrosive to gastrointestinal tract, superoxide radical damage to pulmonary and renal tubular lining cells; increased pulmonary O_2 toxicity; paraquat cations are reduced by NADPH to cation radicals that chain-react with lung O_2 to form superoxide anion radicals, especially in hyperoxic environments.
- Onset: Immediate gastrointestinal effects = nausea, vomiting, diarrhea; subacute ATN in 1–5 days.
- Symptoms: Severe gastrointestinal mucosal ulceration, esophageal perforation, hemorrhagic pulmonary edema, “diphtheritic membrane,” late pulmonary fibrosis from oxygen superoxide radical toxicity.
- Treatment: No antidote; administer immediate adsorbent = AC > Fuller’s earth > bentonite; no emesis or lavage secondary due to increased gastrointestinal perforation risks; sorbitol cathartic; consider bilateral lung transplantation; maintain a very reduced FIO_2 because of the heightened risks of oxygen toxicity.

Diquat

- Diquat: same as paraquat, but not taken up by alveolar lining cells, consequently less lung injury, oxygen toxicity, and residual fibrosis.

Chlorophenoxyacetic Acid Herbicides

- Representatives: 2,4-D and 2,4,5-T = di- and trichlorophenoxyacetic acids; Agent Orange = 2,4-D and 2,4,5-T mixture with dioxin (TCDD) as a contaminant or an adhesive additive: causes chloracne, elevated liver function tests (LFTs), probably carcinogenic.
- Mechanism: Rapid gastrointestinal absorption of fat-soluble acids that target muscle and CNS and uncouple oxidative phosphorylation, like acetylsalicylic acid (ASA or aspirin).
- Onset: Acute gastrointestinal toxicity (nausea, vomiting, diarrhea), then muscle twitching, seizures, and coma.
- Symptoms: Muscular weakness, twitching, seizures, tachycardia, hypotension, hyperthermia, and metabolic acidosis.
- Treatment: No antidote; orogastric lavage and AC, alkaline diuresis with $NaHCO_3$ to trap weak acids in blood and urine.

Volatile Organic Chemical (VOC) Poisoning

Chapter Outline

Hydrocarbons (HCs)

Petroleum distillates

Wood distillates

Toxic volatile alcohols

Anion gap metabolic acidosis

Osmol gap metabolic acidosis

Ethanol

Isopropanol

Ethylene glycol

Methanol

Hydrocarbons (HCs)

Petroleum Distillates

HC Classification

- Mostly petroleum distillates:
 - Acetone and toluene
 - Gasoline and benzene
 - Butane and propane
 - Carbon tetrachloride (CCl_4)
 - Methylene chloride
 - Trichloroethane
 - Trichloroethylene (TCE)
 - Tetra(per)chloroethylene (PCE)
 - n-hexane and n-heptane
 - Methyl-isobutyl ketone (MIBK)
- Few wood (pine) distillates:
 - Pine oil
 - Turpentine

HC Uses

- Adhesives and cements
- Fuels and propellants
- Paints and coatings
- Lacquers and varnishes
- Lubricants and oils
- Polishes and waxes
- Paint removers and strippers
- Paint thinners and solvents
- Cleaning (dry cleaning) solution and degreasers
- Spot removers and dry cleaners
- Typewriter correction fluids (Liquid Paper®)

HC Epidemiology

- There are 60,000 HC exposures per year; 95% are unintentional; 60% involve children; 50% demonstrate minimal toxic effects; and 20% require treatment.

- There are 20 deaths per year from HC poisoning; 90% of these deaths occur in children under age 5; 30% of these deaths involve gasoline/motor oils; and 10% involve Freon® and propellants (usually in adolescent HC inhalation abusers).

HC Toxicology

- Pulmonary toxicity predominates: Pulmonary (50%) > gastrointestinal (5%) > CNS (3%) > cardiovascular > dermal > hematological toxicity.
 - Pulmonary toxicity following aspiration causes reduced alveolar surfactants and adult respiratory distress syndrome (ARDS).
 - HC pulmonary toxicity: Determined by HC physical properties: (1) reduced surface tension, (2) low viscosity, and (3) increased volatility.
 - Symptoms: Gagging, coughing, choking then bronchospasm, rales, rhonchi, tachypnea, hypoxia; subsequent hemorrhagic pulmonary edema, methemoglobinemia (nitro-, nitrites), cyanosis; later chronic upper respiratory infections (URIs), bronchiectasis and pulmonary fibrosis.
 - X-ray: Pneumonitis, infiltrates, consolidating pneumonias, pleural effusions, barotrauma, upright gastric “double-bubble” sign = (1) air–HC interface, (2) HC–gastric fluid interfaces.
- Gastrointestinal (5%): Nausea, vomiting, hematemesis, gastrointestinal mucosal ulcerations.
- CNS (3%): Seizures, then coma, hypoxia on inhalation of volatile HC — often act as “anesthetics” with progression from Stage II (excitement) to Stage IV anesthesia (coma).
- Cardiovascular: Myocardial sensitization to catecholamines, tachydysrhythmias.
- Dermal: Defatting dry dermatitis, oil boils, degreaser’s flush (especially trichloroethylene).
- Hematological: Methemoglobinemia, hemolysis, anemia, DIC.

HC Treatment

- Careful gastrointestinal decontamination: No emesis! No activated charcoal! Possibly gastric lavage with small nasogastric for large volumes, intentional ingestions, and highly toxic HCs: (CHAMP) = the highly toxic HCs: camphor, halogenated HCs, aromatic HCs, HCs associated with metals, HCs associated with pesticides.
- No cathartics, especially no olive or mineral oil cathartics (increase absorption of lipid-soluble HCs), no prophylactic antibiotics or corticosteroids.
- Mechanical ventilation for ARDS: Barotrauma risk = start with low positive-end expiratory pressures (PEEP) > high-frequency jet ventilation (HFJV) > extracorporeal membrane oxygenation (ECMO).
- Cardiovascular: Consider avoiding inotropic support, unless indicated, due to myocardial sensitization and increase risks of arrhythmogenesis.

Volatile Substance Abuse

- Techniques: Sniffing → huffing → bagging of vapors of volatile HCs.
- Agents: Toluene (glues, paints) → fuels (butane, gasoline) → TCE and PCE (typewriter correction fluids, Liquid Paper®) → dry-cleaning fluids (acetone, CCl₄, TCE, PCE).
- Acute toxicity: CNS — excitation, euphoria, hallucinations, ataxia, seizures, headache, respiratory depression > cardiovascular — tachyarrhythmias → “sudden sniffing death” > hematologic methemoglobinemia > hepatotoxicity (CCl₄) and CO poisoning (methylene chloride).
- Chronic toxicity: “Glue-sniffers” encephalopathy/chronic “painter’s syndrome”: neuropsychiatric disorders characterized by memory and cognitive losses, dementia, insomnia, anxiety and depression, personality disorder, ataxia and chorea, peripheral neuropathy (particularly following n-hexane and MIBK exposures).

Wood Distillates

Pine Oil

- PineSol®.
- Pine terpenes.
- Toxicity: Pulmonary > CNS.
- Pulmonary: Aspiration pneumonitis.
- CNS excitation → depression.
- Treatment: Same as for the petroleum distillates.

Turpentine

- Pine terpenes.
- Toxicity: Pulmonary > renal > hematologic > CNS:
 - Pulmonary: Aspiration pneumonitis.
 - Renal: Pathognomonic of turpentine = hemorrhagic cystitis → possible ATN.
 - Hematologic: Pathognomonic of turpentine = thrombocytopenic purpura (TP).
 - CNS: Excitation → depression.
- Treatment: Same as for petroleum distillates.

Toxic Volatile Alcohols

Anion Gap Metabolic Acidosis

- Definition: $[\text{Measured cations} - \text{measured anions}] = [\text{Na}^+] - [\text{Cl}^- + \text{HCO}_3^-] = 140 - [110 + 24] = 6$.
- Normal range: 3–11.
- High anion gap metabolic acidosis: MUD-PIILESS = methanol, uremia, diabetic ketoacidosis, paraldehyde, phenformin, INH, iron, lactic acidosis, ethanol, ethylene glycol, salicylates, and solvents.
- Low anion gap metabolic acidosis: Bromides can cause falsely elevated chloride levels and induce a factitious low anion gap metabolic acidosis.

Osmol Gap Metabolic Acidosis

- Definition: $[\text{Measured osmolality} - \text{calculated osmolality}] = [\text{mOsm/kg}] - [2\text{Na}^+ + \text{Glu}/18 + \text{BUN}/2.8] = -14 \text{ to } +10$.
- Normal range: -14 to +10.
- High osmol gap metabolic acidosis: Ethanol, all toxic alcohols, lactic acidosis, renal failure, hyperlipidemias, hypertriglyceridemias, and hyperproteinemias (multiple myeloma).

Ethanol

Ethanol Pharmacology and Toxicity

- Chemistry: Colorless, odorless hydrocarbon; highly water-soluble and highly lipid-soluble; dependence and addiction possible.
- Pharmacology: Low molecular weight, low $V_d = 0.6 \text{ L/kg}$, rapidly diffusible; rapid gastric emptying and drinking without food increase absorption; hepatically oxidized by three pathways: (1) volume of distribution (V_d) alcohol dehydrogenase (ADH) ($\text{EtOH} \rightarrow \text{ADH} \rightarrow \text{acetaldehyde} \rightarrow \text{acetaldehyde DH} \rightarrow \text{acetyl CoA} \rightarrow \text{thiamine cofactor}$, then Krebs's TCA cycle and $\text{CO}_2 + \text{H}_2\text{O}$) > (2) CYP-450 (inducible metabolism) > (3) hepatic metabolism catalyzed by peroxidase catalase.

- Toxicity: CNS > gastrointestinal > metabolic:
 - CNS: Inebriation, disinhibition, incoordination, blurred vision, diplopia, confusion, CNS and respiratory depression.
 - Gastrointestinal: Nausea, vomiting, cramping abdominal pain, gastric bleeding.
 - Metabolic: High-anion gap metabolic acidosis, hypoglycemia, hypokalemia, hypomagnesemia, hypophosphatemia, hyperamylasemia.

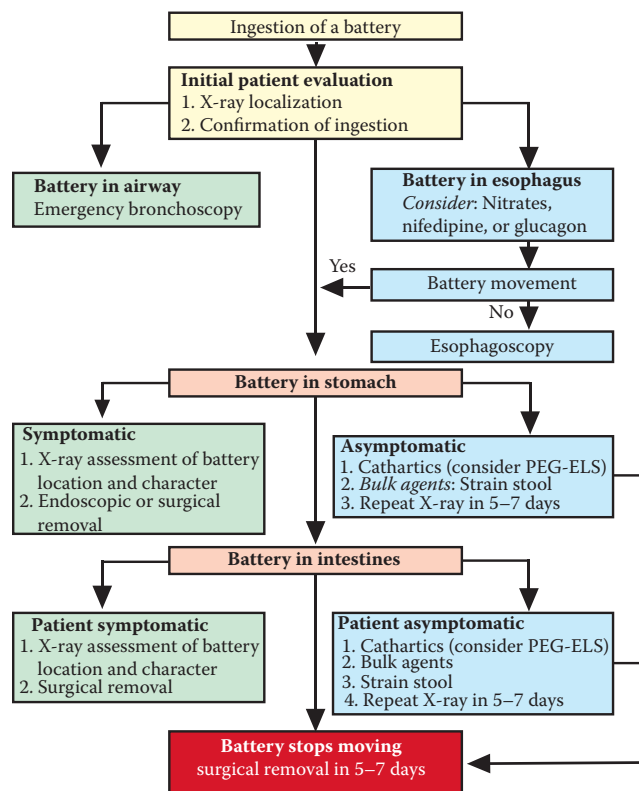


FIGURE 20.1 Ethylene Glycol Metabolism. The hepatic biotransformation reactions, which are responsible for the metabolism of ethylene glycol, a common component of antifreeze.

Acute Ethanol Intoxication

- Blood ethanol levels
 - 0.05% (50 mg/dL)
 - 0.10% (100 mg/dL)*
 - 0.20% (200 mg/dL)
 - 0.30% (300 mg/dL)
 - 0.40% (400 mg/dL)
 - 0.70% (700 mg/dL)

[* Legally intoxicated, 0.08–0.10%]

Clinical Manifestations

- Disinhibition and incoordination.
- Reduced reaction time, auto driving impaired.
- Nausea, vomiting, confusion, staggering gait.
- Slurred speech, decreased vision and decreased sensation.
- Reduced temperature, low glucose, amnesia, seizures.
- Reduced deep tendon reflexes (DTRs), respiratory depression, loss of airway protective reflexes, aspiration pneumonia, coma, death.

Ethanol Overdose Diagnosis

- Blood ethanol levels: Determine stage of intoxication.
- Blood glucose: Rule out hypoglycemia.
- CBC and electrolytes: Low Na, K, Mg, Ca, and P.
- ABGs: High-anion gap metabolic acidosis.
- Serum amylase: Rule out concomitant acute pancreatitis.
- Serum ammonia: Rule out hepatic encephalopathy from cirrhosis.

Ethanol Overdose Management

- Ipecac contraindicated.
- Orogastric lavage and AC: Especially for co-ingestions.
- Coma cocktail: D₅₀W, 0.5–1.0 g/kg, and thiamine, 100 mg IV.
- Multivitamins and folate, 1–5 mg IV.
- Slow rewarming.
- Correct electrolytes: Low K-Mg-P.
- Enhanced elimination: Hemodialysis very effective because of low molecular weight and V_d, but rarely indicated.

Ethanol Antabuse Reactions

- Antabuse reaction: Flushing, diaphoresis, nausea, vomiting, disorientation, vertigo, headache, palpitations, chest pain.
- Antibiotics: Chloramphenicol, n-MTT side-chain cephalosporins, sulfonamides.
- Antifungals: Griseofulvin, metronidazole.
- Mickey Finn: Chloral hydrate (and its trichloroethanol metabolite).
- Miscellaneous: *Coprinus* spp. mushrooms, industrial chemicals: carbamate pesticides and oximes.

Isopropanol

Isopropanol Pharmacology and Toxicity

- Chemistry: 70% isopropyl alcohol or rubbing alcohol; a clear, colorless volatile liquid with an acetone smell; used in toiletries, disinfectants, window cleaners, and solvents. Exception: adsorbed by AC.
- Pharmacology: Rapid all-route absorption, especially dermal and inhalation; low V_d = 0.6 L/kg; 80% rapidly metabolized by ADH to acetone, remaining 20% unmetabolized and excreted by kidneys > exhalation.
- Toxicity: CNS > gastrointestinal > pulmonary > metabolic:
 - CNS: 3× more CNS depression than EtOH, lethargy, weakness, headache, ataxia, apnea, respiratory depression, hypotension.
 - Pulmonary and gastrointestinal: Acetone breath, hemorrhagic gastritis and hemorrhagic tracheobronchitis.
 - Metabolic: Exception: only toxic alcohol not causing metabolic acidosis or hypoglycemia, euglycemia, ketonemia then ketonuria.

Isopropanol Overdose Diagnosis and Management

- Determine serum acetone level.
- Anticipate falsely elevated creatinine.
- ABGs: pH will be normal, no metabolic acidosis, no anion gap.
- Glucose: No hypoglycemia.
- Anticipate ketonemia and ketonuria due to acetone.
- Breath: Acetone odor.

- Management:
 - Immediate skin decontamination.
 - Orogastric lavage, then AC. Exception: only toxic alcohol to be well adsorbed by AC.
 - Enhanced elimination: Hemodialysis very effective in serious overdoses, especially in children.

Ethylene Glycol

Ethylene Glycol Pharmacology and Toxicity

- Chemistry: A toxic alcohol similar to methanol in toxicity and lethality with a characteristic delayed onset of toxicity; used in antifreeze (95%), refrigerating fluids, fire extinguishers, solar energy fluids.
- Pharmacology: Rapidly absorbed orally, peaks in 1–4 hours; rapidly metabolized by alcohol dehydrogenase (ADH) to glycoaldehyde; then to glycolic, glyoxalic, and oxalic acids. Pyridoxine and thiamine serve as cofactors to promote nontoxic alternative routes of metabolism.
- Toxicity: (1) CNS > (2) metabolic > (3) renal > initial gastrointestinal nausea and vomiting.
- Toxic phases 1–3:
 - Phase 1: CNS: nausea, vomiting, intoxication, inebriation, nystagmus, myoclonus, seizures, progressing to lethargy and coma in 4–8 hours.
 - Phase 2: Metabolic: profound high anion gap metabolic acidosis causing cardiovascular collapse.
 - Phase 3: Renal: urinary excretion of toxic metabolites (calcium oxalate and hippuric acid); calcium oxalate crystalluria, nephrolithiasis, proteinuria and hematuria, then acute tubular necrosis (ATN).

Ethylene Glycol Overdose Diagnosis and Management

- Diagnosis: Calcium oxalate crystalluria, urine fluorescein staining under ultraviolet Wood's lamp, serum EG levels by gas chromatography.
- Initial management: AC ineffective due to rapid absorption and delayed symptoms onset of 4–8

hours; ipecac contraindicated due to vomiting; NaHCO_3 to correct acidosis and to promote increased excretion weak acids; antidotes = ethanol (and/or 4-methylpyrazole [4-MP]) as preferred ADH substrates, 0.8 g/kg IV or 8 ml/kg orally, to maintain serum EtOH level of 100–150 mg/dL (EG:EtOH ratio = 1:4).

- Enhanced elimination: (1) Urinary alkalization to promote urinary excretion of weak acid metabolites; (2) thiamine, 100 mg IV, and pyridoxine, 50 mg IV, every 6 hours, to promote alternative nontoxic routes of metabolism; (3) hemodialysis for EG levels >25 mg/dL.
- Correct hypocalcemia: treat hypocalcemia due to massive calcium losses from calcium oxalate crystalluria.

Methanol

Methanol Pharmacology and Toxicity

- Chemistry: Methyl alcohol or wood alcohol; used in windshield washing fluids, deicing solutions, carburetor cleaners, model airplane and canned heat (Sterno®) fuels, paint removers/thinners.
- Pharmacology: Rapid all-route absorption, peaks 0.5–1 hour; 85% rapidly metabolized by hepatic ADH to formaldehyde and formic acid metabolites that are responsible for retinal toxicity.
- Toxicity: Eye/CNS > metabolic > initial gastrointestinal — nausea, vomiting, and cramping.
 - Eye: Dimmed and blurred vision, scotomata, dilated and sluggishly reactive pupils, hyperemic optic discs, retinal edema, blindness.
 - Metabolic: 24 hours delayed onset of high anion gap metabolic acidosis, followed by oculotoxicity.
 - CNS: Inebriation, headache, vertigo, meningismus, seizures, coma.

Methanol Overdose Diagnosis and Management

- Diagnosis: Lactic acidosis, unique eye findings, increased serum levels by gas chromatography.
- Initial management: AC ineffective due to rapid absorption and delayed symptom onset; ipecac contraindicated due to vomiting; NaHCO_3 to correct acidosis; antidotes = ethanol (and/or 4-

MP) as preferred ADH substrates, 0.8 g/kg IV or 8 ml/kg orally, to maintain serum EtOH level 100–150 mg/dL (Meth:EtOH ratio = 1:4).

- Enhanced elimination: (1) Urinary alkalinization to promote renal excretion of undissociated formic acid; (2) folic acid, 150 mg IV every 4 hours, to serve as a cofactor promoting the metabolism of formic acid to $\text{CO}_2 + \text{H}_2\text{O}$; (3) hemodialysis for methanol levels >25 mg/dL.

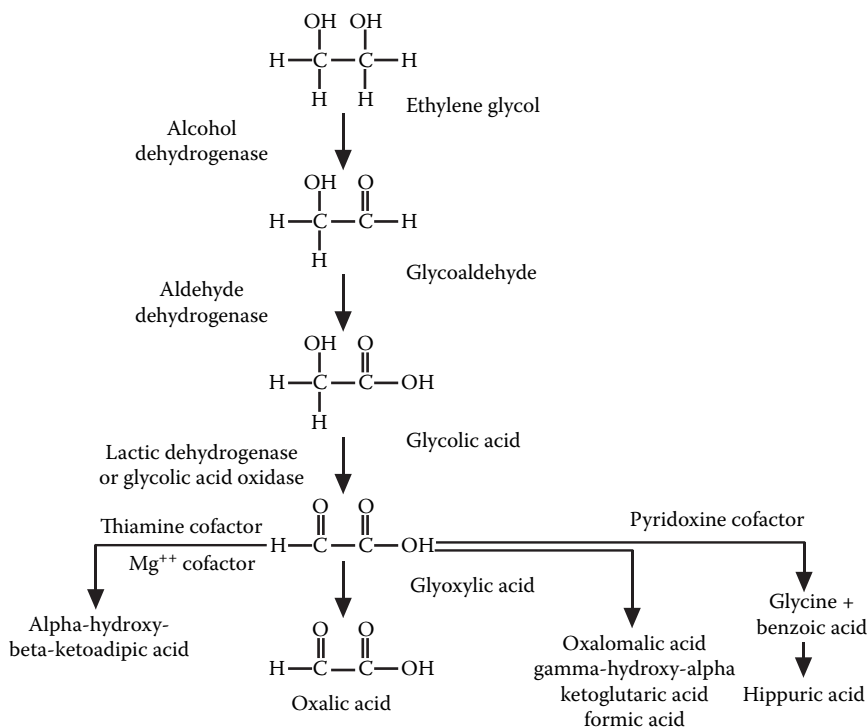


FIGURE 20.2 Methanol metabolism. The hepatic biotransformation reactions, which are responsible for the metabolism of methanol or wood alcohol.

FIGURE 20.3 Methanol metabolism. The hepatic biotransformation reactions, which are responsible for the metabolism of methanol or wood alcohol.

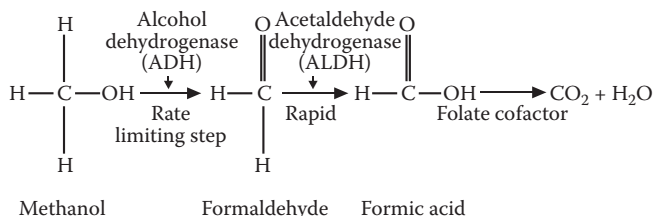


TABLE 20.1 Pathophysiology and Management of Toxic Alcohol Poisonings

Alcohol	Uses	Toxic Dose	Action Level	Metabolism	Manifestations	Management
Isopropanol (rubbing alcohol)	Rubbing alcohol Nail polish remover	2–4 mL/Kg	NA	Metabolized by ADH to acetone — exhaled or urine excreted	Ketosis without acidosis Inebriation Ataxia Dysarthria Confusion Stupor, coma Acetone breath Hemorrhagic gastritis	Supportive No ethanol
Ethylene glycol (antifreeze)	Antifreeze Coolants Brake fluids	1–1.5 mL/Kg	>20–20 mg/dL	Metabolized by glycolic and oxalic acids Oxalate combines with calcium to cause calcium oxalate crystalluria	Increase anion and osmolar gaps Hypocalcemia with prolonged QT and tertiary 1) CNS (1–12 hours) ataxia, nyctagmus, seizures, nausea, vomiting 2) CV/ metabolic (12–72 hours) hypertension, tachycardia, prolonged QT, CV collapse 3) Renal (24–72 hours) CVA, tenderness, oliguria, urine fluorecein, acute renal failure	Alkalinize urine Thiamine and pyridoxine to promote nontoxic metabolism Ethanol IV or 4- methyl-pyrazole orally Hemodialysis
Methanol (wood alcohol)	Windshield washer fluid Radiator fluid Sterno® fuel	<1 mL/Kg	>50 mg/dL	Metabolized by ADH to formaldehyde and formic acid	Increased anion and osmolar gaps Intoxication Nausea, vomiting Hemorrhagic gastritis Photophobia Blurred/reduced vision “Snowfield” blindness Retinal edema Hyperemic optic disks	Alkalinize urine Folic acid to promote nontoxic metabolism Ethanol IV Hemodialysis

Heavy Metal Poisoning

Chapter Outline

Arsenic (As)

- Forms of Arsenic
- Uses (inorganic arsenics)
- Toxicology
- Pathophysiology
- Clinical effects
- Diagnosis
- Treatment

Cadmium (Cd)

- Uses of cadmium
- Exposures
- Toxicology
- Pathophysiology
- Clinical effects
- Diagnosis
- Treatment

Chromium (Cr)

- Uses of chromium
- Exposures
- Toxicology
- Pathophysiology
- Clinical effects
- Diagnosis
- Treatment

Lead (Pb)

- Uses of lead — inorganic and organic
- Sources of lead exposure
- Toxicology
- Pathophysiology
- Diagnosis
- Treatment

Mercury (Hg)

- Forms and exposures of mercury
- Toxicology
- Pathophysiology
- Clinical syndromes
- Methyl mercury poisoning and acrodynia
- Diagnosis and management

Thallium

- Properties of thallium
- Uses and exposures of thallium
- Toxicology
- Pathophysiology
- Differential diagnosis: Alopecia and Mees lines

Minor metal toxicity

- Nickel
- Cobalt
- Copper
- Manganese
- Selenium
- Tin
- Zinc

Arsenic (As)

Forms of Arsenic

- Elemental: Nontoxic if ingested.
- Gaseous: Arsine gas — highly toxic, causes adult respiratory distress syndrome (ARDS), followed by acute hemolysis and acute tubular necrosis (ATN) with high case fatality rates (CFRs).
- Inorganic: Arsenic trioxide — As+3, and pentoxide — As+5.
- Organic: Nontoxic, concentrated by shellfish, especially oysters.

Uses (Inorganic Arsenics)

- Pesticides: As+3:
 - Wood preservatives
 - Outdoor furniture and play equipment
 - Antiparasitics
 - Fungicides and herbicides
- Electronics manufacture:
 - Semiconductors (gallium arsenide coatings)
- Folk remedies:
 - Depilatories and elixirs

Toxicology

Absorption/Distribution

- Tasteless and odorless.
- Well absorbed rapidly.
- Pulmonary (especially arsine gas) > gastrointestinal (inorganics) > dermal absorption.
- Systemic distribution, especially to liver and kidneys, but also to skin, hair, and nails.
- Can remain as radiopaque metal sludge in small intestine and enter enterohepatic circulation.

Metabolism/Excretion

- Rapid hepatic methylation to methylarsonic acid (MAA) and dimethylarsinic acid (DMA) — methylation requires glutathione.

- Glutathione depletion: Common in alcoholics and malnourished, will reduce arsenic's metabolism by methylation and increase its toxicity.
- Renal excretion (90%) > gastrointestinal-fecal > dermal — hair and nails.

Pathophysiology

- Reduced glucose production resulting from inhibition of pyruvate dehydrogenase with impaired gluconeogenesis.
- Reduced glucose uptake and utilization.
- Decreased production of ATP.
- Rapid glucose depletion with severe hypoglycemia, especially in the central nervous system (CNS) and peripheral nervous system (PNS).

Clinical Effects

Acute Toxicity

- Gastrointestinal: Initial symptoms = metallic taste, garlic breath, nausea, vomiting, cramps, rice-water (cholera-like) diarrhea.
- Cardiovascular: Blood pressure instability, orthostasis, ECG changes: prolonged QT interval and T wave changes.
- CNS: Encephalopathy, seizures, coma.
- Pulmonary: ARDS and respiratory failure (RF).
- Hepatorenal: Rhabdomyolysis + acute hemolytic anemia may lead to acute tubular necrosis (ATN), especially in the glutathione-depleted (alcoholics and malnourished).

Chronic Toxicity

- PNS: Glove and stocking peripheral sensory neuropathy, reduced pain-touch-position-temperature-vibration sensation, reduced deep tendon reflexes may lead to ascending flaccid

paralysis; partial sensorimotor recovery only, even after chelation.

- CNS: Encephalopathy, cranial nerve palsies, dementia.
- Dermal: Hyperpigmentation and hyperkeratosis may progress to skin cancer (squamous and basal cell carcinoma, Bowen's disease), Mees' lines on fingernails.
- Pulmonary: Lung cancer

Diagnosis

- Labs: Urine spot arsenic (As) + 24-hour urine As.
- Rule out shellfish ingestion and nontoxic organic arsenic exposure by liquid separation chromatography.
- CBC, liver function tests, renal function tests (RFTs), hair and nail As levels.
- X-rays: Flat abdomen for radiopaque sludge in stomach and small intestine.

Treatment

- Orogastric lavage if radiopaque sludge present, then whole-bowel irrigation (WBI) with polyethylene glycol–electrolyte (PEG-ELS) solution.
- Intravenous glucose and nutritional support.
- Monitor for respiratory failure using negative inspiratory force (NIFs) measurements.
- Chelation: British anti-Lewisite (BAL) IM > succimer orally > penicillamine orally.
- Hemodialysis for ATN.

Cadmium (Cd)

Uses of Cadmium

- Electroplating: silverware.
- Glazing: Pots, pans, utensils.
- Soldering: Hot and cold vending machines.
- Batteries: Nickel-cadmium.
- Paint pigments.
- Film manufacture.

Exposures

- Vapor and fume inhalation: Occupational.
- Ingestion: Acidic foods and liquids contaminated by cadmium (Cd)-glazed containers and pitchers.

Toxicology

Absorption/Distribution

- Inhalation > gastrointestinal absorption.
- Rapid transport to liver for binding with its specific metal transport protein, metallothionein.
- Circulatory transport of bound Cd to kidneys for glomerular filtration and proximal tubular reabsorption.
- Bound Cd concentrated in kidneys > bone > liver.

Metabolism/Excretion

- Not biotransformed.
- As hepatic and then renal metallothionein production is overwhelmed, unbound Cd is distributed to kidneys and bone, where it establishes a reservoir pool (like lead in bone).
- Slow renal elimination with $T_{1/2} = 7-30$ years.

Pathophysiology

- Once the stores of metallothionein binding protein are depleted and the hepatorenal protein synthesizing capabilities are overwhelmed, free toxic Cd is distributed to kidneys > bone > liver.
- Chronic Cd nephrotoxicity causes a Fanconi's syndrome of aminoaciduria, glucosuria, and phosphaturia with reduced renal urine concentrating ability and altered excretion of Ca and P with nephrolithiasis.
- Urinary calcium loss results in osteomalacia with pathologic bone fractures ("itai-itai" or "ouch-ouch" disease).
- Chronic inhalation exposure causes emphysema and pulmonary fibrosis.
- Cd workers have a higher incidence of prostate and lung cancers.

Clinical Effects

Acute Toxicity

- Gastrointestinal: Nausea, vomiting, diarrhea.
- Pulmonary: Acute chemical pneumonitis > "metal fume fever," which may be associated with pulmonary acute edema and later ARDS.
- Renal: Proximal tubular dysfunction, glucosuria, and proteinuria = Fanconi's syndrome.

Chronic Toxicity

- Pulmonary: Emphysema, pulmonary fibrosis, lung cancer.
- Genitourinary/renal: Reduced GFR, chronic renal failure, nephrolithiasis, prostate cancer.
- Bone: Demineralization, osteomalacia, pathologic fractures ("itai-itai" or "ouch-ouch" disease).

Diagnosis

- Urine > serum Cd.
- Serum Cd: Unhelpful and not reflective of body burden as Cd is protein bound to metallothionein in kidneys > liver.
- Urine metallothionein levels.
- Increasing proteinuria and glucosuria, reflecting early Fanconi's syndrome.

Treatment

- Gastric evacuation and catharsis.
- Pulmonary support.
- Chelation contraindicated as it will increase renal cadmium load and further deplete metallothionein carrier protein levels, increasing Cd toxicity.

Chromium (Cr)

Uses of Chromium

- Cement mix
- Electroplating
- Alloys
- Chrome yellow paint pigment
- Wood preservatives
- Leather tanning

Exposures

- Mining
- Stainless steel machining
- Chrome-plating
- Refrigeration plumbing

Toxicology

Absorption/Distribution

- Toxicity increases with valency of Cr.
- Hexavalent Cr^{6+} is more toxic than the relatively nontoxic and insoluble trivalent Cr^{3+} .
- Inhalation–pulmonary > ingestion–gastrointestinal > transdermal absorption.
- Concentrated in lungs > kidneys > liver.

Metabolism/Excretion

- Not metabolized.
- Soluble hexavalent Cr^{6+} is oxidized and reduced on entering the body to trivalent Cr^{3+} , which is trapped in red blood cells for 120 days.
- Excretion is primarily renal > bile and feces > sweat, hair, nails, breast milk.

Pathophysiology

- Caustic, soluble hexavalent chromium is rapidly absorbed, particularly by the lungs.

- As soon as hexavalent chromium enters the body, it is reduced to insoluble trivalent chromium, which is trapped within red blood cells until they expire in 120 days.
- Hexavalent chromium is more readily absorbed and concentrated in the airways and lungs, where it acts as a pulmonary irritant, sensitizer, and carcinogen.

Clinical Effects

Acute Toxicity

- Pulmonary: Caustic irritation–burning, acute bronchitis, rhinitis, sinusitis, mucosal ulceration, nasal septal perforation.
- Skin: Caustic thermal burns and ulcerations = “chrome holes.”
- Renal: Hemolytic anemia with hemoglobinuria, proximal tubular damage (Fanconi’s syndrome), ATN.
- Hepatic: Hepatotoxicity.

Chronic Toxicity

- Pulmonary: Chronic bronchitis, rhinitis, sinusitis, nasal septal perforation, occupational asthma, pneumoconiosis, nasal and lung cancers.
- Skin: Non-healing chrome holes, irritant dermatitis.
- Renal: Chronic interstitial nephritis, chronic renal failure.

Diagnosis

- Urine > blood chromium levels.
- Avoid provocative skin patch testing as it frequently causes skin sensitization to future chromium exposures.

Treatment

- Immediate decontamination: Remove clothing and shower.
- Induced vomiting contraindicated as Cr^{+6} is a strong caustic alkali.
- 10% topical ascorbic acid (vitamin C) to (1) reduce Cr^{+6} to nontoxic Cr^{+3} then (2) chelate reduced Cr^{+3} with topical 10% CaNa_2EDTA .
- Consider careful nasogastric lavage with oral ascorbic acid and NAC, followed by IV ascorbic acid and oral NAC for severe poisoning.

Lead (Pb)

Uses of Lead — Inorganic and Organic

Uses of Inorganic Lead

- Lead arsenate — insecticide
- Lead azide — bullet primers
- Lead carbonate — white (light) paints
- Lead chromate — yellow (pastel) paints
- Lead oxide — red (dark) and all rust-proof and marine (ships and bridges) paints
- Lead silicate — ceramic glazes
- Lead sulfide — natural ore — galena

Uses of Organic Lead (antiknock gasoline additives)

- Tetraethyl lead: U.S. gasoline additive until 1978.
- Tetramethyl lead: U.S. gasoline additive until 1978.
- Antiknock additives: Replaced by methyl-tertbutylether (MTBE) (leaking underground storage tanks epidemic), but still in use for agricultural and military vehicles and all vehicles in the developing world.
- Organic lead poisoning: Results from work exposures or recreational sniffing of gasoline with toxicity resulting from the metabolites or the organic leads, primarily triethyl lead, which causes symptoms resembling the CNS manifestations of inorganic lead poisoning. Inorganic lead biomarker levels are of no use in assessing severity of organic lead poisoning. Management of both forms of lead poisoning is similar.

[* Leaking underground storage tanks]

Sources of Lead Exposure

Primary Sources

- Paints: Now cracking and peeling off; 3 million tons per year, 57 million pre-1980 buildings.
- Soil: Paint residues (“yuppie plumbism”), leaded gas emissions and lead recycling/smelting emissions.
- Water: Lead pipes and solder in pre-1980 buildings; lead glazed crystal, cooking utensils, pots, water coolers.

Secondary Sources

- Air: 500 tons released/year from battery and radiator recycling and approved agriculture/military leaded gasoline uses.
- Food: 1% of cans and containers may contain lead = lead-soldered cans, animal bone — natural Ca supplements, alcohol leaching lead in lead-crystal decanters, acidic juices leaching lead in ceramic glassware, bootleg whisky with lead from radiator and lead pipe stills.

Exotic and Underreported Lead Exposures

- Folk remedies and homemade “candies”: In every ethnicity (especially Hispanic = Mexican and Cuban, Indian, SE Asian). Example: “*greta*” and “*azarcon*” as prominent indigestion recipes, after-dinner “mints,” and antidiarrheal agents (mechanisms: induced autonomic neuropathy with resulting dynamic ileus).
- Retained bullets and shrapnel, especially in joint or pleural spaces.
- Ingested foreign bodies.
- Gasoline (leaded) huffing.
- Many hobbies: ceramics, painting, stained glass, target shooting, bullet/cartridge reloading, auto and boat repairs, model boat building.

TABLE 21.1 Lead Toxicology

Absorption	Distribution	Excretion
Adults: inh > GI (occupational)	1st blood pool, 99% rbc bound	Urine > bile > sweat > hair
Particles <1 μ m	Labile ST pool	Urine 65%
Inh 30–40%	Stable ST pool brain > kidney > liver	Bile 35%
GI 10–15%	Labile trabecular bone pool	T1/2 blood: weeks–months
Children: GI > inh, GI 40–50%	Stable cortical bone pool	T1/2 bone: 10–20 years
Rapid placental transfer		

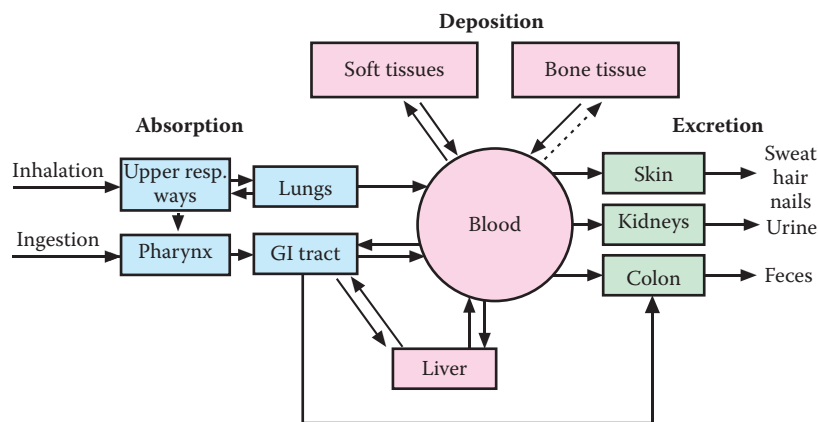
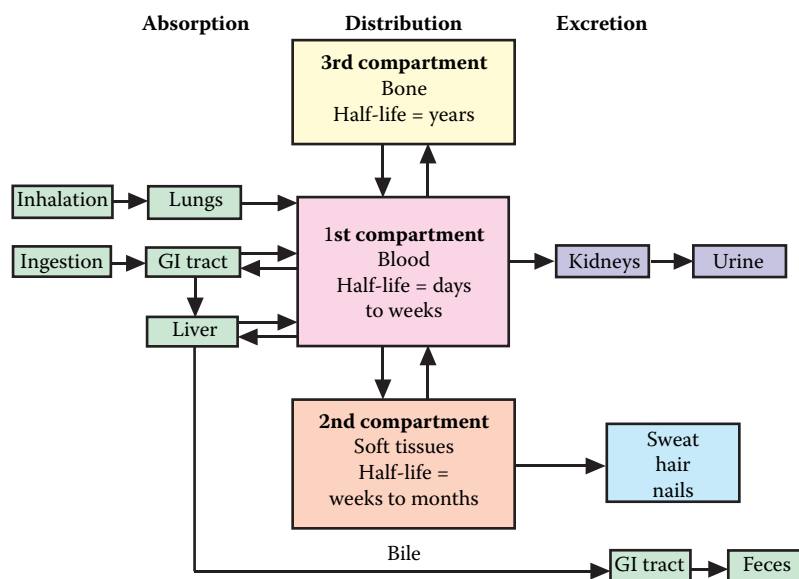


FIGURE 21.1 A biotransformation model for heavy metal poisoning. Heavy metals may be inhaled, ingested, or absorbed through the skin to gain access to the central circulatory compartment for distribution to highly perfused organs for metabolism or biotransformation and excretion. Many heavy metals remain in soft tissues, such as hair and nails, and poorly perfused tissues, such as bone and teeth, for prolonged periods.

FIGURE 21.2 Ingested lead distributes in a three-compartment model. Ingested lead is distributed in a three-compartment model in which the heavy metal is initially distributed to a central circulatory compartment; then to a highly perfused visceral organ compartment; and finally to the least perfused third compartment composed of bone, teeth, nails, and hair.



Pathophysiology

Primary Effects:

- Neurologic
- Hematologic
- Renal
- Reproductive

Secondary Effects

- Endocrine
- Skeletal
- Gastrointestinal
- Cardiac

Lead Neurotoxicity

Central Nervous System (targeted in children)

- Inhibits acetylcholine, dopamine, norepinephrine, gamma-aminobutyric acid (GABA), N-methyl-D-aspartate (NMDA) neurotransmission.
- Targets cortex, cerebellum, and occipital lobes.
- Acute encephalopathy: Increased intracranial pressure, seizures, and coma.
- Children: Hearing, cognition, IQ, developmental, motor, and coordination disorders.

Peripheral Nervous System (targeted in adults)

- Schwann cell necrosis and demyelination (adults).
- Reduced peripheral nerve conduction amplitude and velocity, upper extremity > lower extremity.

- Motor > sensory neuropathy.
- Wrist drop (“dangles”) > foot drop.

Lead Hemotoxicity

Reduced Hemoglobin Synthesis

- Inhibits ALA synthetase, δ -ALA dehydratase (initially), coproporphyrinogen (CPG) decarboxylase and ferrochelatase.
- Normo- to-hypochromic microcytic anemia.
- Organic leads (tetraethyl lead): cause nausea, vomiting, increased deep tendon reflexes (DTRs), tremor and encephalopathy; but do not cause anemia or inhibit heme synthesis.

Reduced RBC Integrity

- Decreased red blood cell (RBC) survival.
- Increased RBC membrane fragility.
- Basophilic stippling of RBCs results from an inhibition of RBC 5'-pyrimidine nucleotidase,

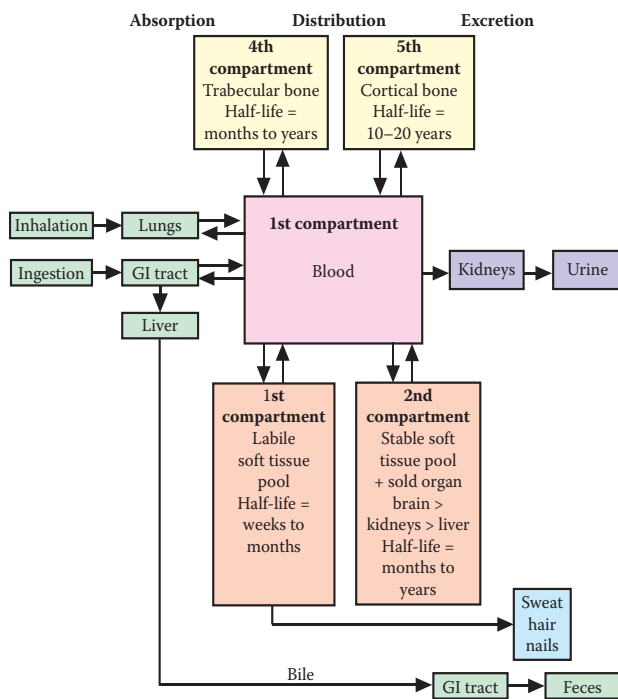


FIGURE 21.3 Ingested lead distributes in a five-compartment model. Distribution models for lead poisoning may be expressed as simple three-compartment models or more precise five-compartment models, which include the added abilities of the cortical and trabecular bone compartments to function as long-term storage compartments for lead.

causing an inability to remove degraded RNA from the RBC, stippling the RBC's inner membrane, which clumps together with damaged mitochondria and microsomal remnants.

Lead Nephropathy

- Adults > children.
- Nuclear inclusions from lead-protein complexes in tubular cells and their casts.
- Fanconi's syndrome: Aminoaciduria, glucosuria, and phosphaturia.
- Chronic renal failure (CRF) secondary to tubular atrophy and fibrosis.
- Renovascular hypertension secondary to increased renin.

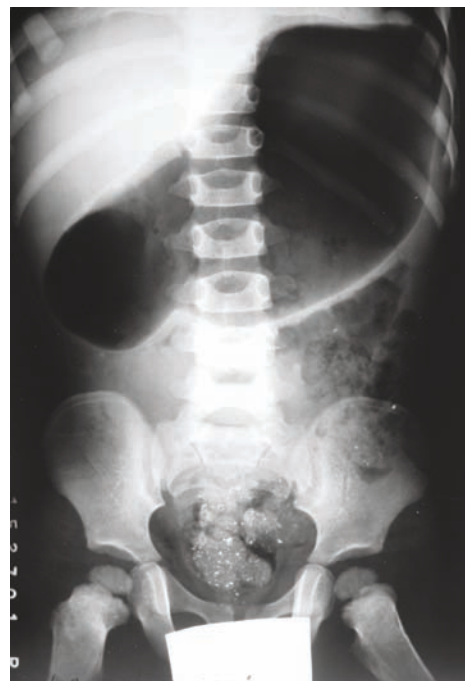


FIGURE 21.4 Non-dissolving radiopacities in the gastrointestinal tract. Abdominal radiograph of a 3-year-old boy with a history of ingesting lead paint chips peeling off doors and windows. Note radiopaque lead paint chips in colon and rectum. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

"Saturnine" Gout

- Saturn: The Roman god of agriculture and vineyards; red wines leach lead out of lead-glazed and leaded glass decanters.
- Adults > children.
- Increased renal uric acid excretion.
- Increased serum uric acid.
- Uric acid crystal deposition in joints (gouty arthropathy), kidneys (urolithiasis), and skin (tophi).

Lead Reproductive Toxicity

- Females: Infertility, stillbirths, prematurity, possible VACTREL* association birth defects.
- Males: Infertility from reduced sperm motility and counts, abnormal sperm morphology.

[* VACTREL: Congenital constellation of vertebral, anal, cardiac, tracheo–esophageal fistula (TEF), limb, and genital anomalies.]

Lead Secondary Toxicities

Endocrinopathy

- Adults: Hypothyroidism.
- Children: Decreased growth hormone secretion and short stature, decreased adrenopituitary axis function.

Lead Skeletal Effects (children)

- Reduced osteoblast and osteoclast function.
- Lead lines at pediatric metaphyses, long bones — results from initial arrested bone growth followed by rapid bone growth with hypermineralization.
- Reduced bone growth and short extremities and stature in children.

Lead Cardiac Effects (adults)

- Systolic hypertension.
- Dysrhythmias.

Lead Gastrointestinal Effects

- Metallic taste in mouth.
- Lead colic: Abdominal pain, vomiting, constipation (mechanism: colonic autonomic neuropathy).
- Burton's lines: Gingival–dental line lead sulfide deposits.
- Acute exposure: Hepatitis and pancreatitis, especially in adults.

TABLE 21.2 Clinical Findings: Children

Severity	Severe	Moderate	Asymptomatic
Blood lead levels	>70–100	>50–70	>10 mcg/dL
CNS	Increased ICP, CN palsies, encephalopathy	Irritable-to-lethargic "difficult" child	Reduced cognition, bizarre behavior, loss of hearing and coordination
Gastrointestinal	Persistent vomiting	Anorexia, lead colic	From none to constipation
Hematologic	Anemia	rbc stippling	rbc stippling

TABLE 21.3 Clinical Findings: Adults

Severity	Severe	Moderate	Mild
Blood lead levels	>100–150	>80	>40 mcg/dL
CNS	Encephalopathy, wrist > foot drop	Headache, loss of memory, infertility	Somnolence, disinterested affect
Gastrointestinal	Lead colic	Constipation	Metallic taste
Hematologic/Cardiovascular	Anemia, pallor, systolic HTN	Anemia, HTN	HTN
Renal	CRF, gout	Nephropathy	None

Diagnosis

Laboratory Studies

- Normochromic–hypochromic microcytic anemia.
- Basophilic stippling of RBCs.
- U/A: Increased protein and glucose.
- Biomarkers: Serum > urine; increased urine δ -ALA, blood lead > erythrocyte protoporphyrin (EP) > zinc protoporphyrin (ZPP) + free erythrocyte protoporphyrin (FEP) (EPs and ZPP insensitive at blood lead levels 10–25 mcg/dL).
- Urine, hair assays insensitive.
- Tooth assays impractical.

Radiographic Images

- Long bones (children): Metaphyseal lead lines of increased calcification at wrists (radius), hips (femur), and knees (tibia).
- Flat abdomen: Radiopaque ingestions of metal foreign bodies, paint chips, folk medicines; adynamic ileus with dilated bowel.
- CT: Cerebral edema, reduced gray-white matter demarcation.
- MRI: Cortical atrophy, cerebral infarcts.

Treatment

Reduce Lead Exposures

- Reduce pre-exposures risks: Children and pregnant > adults; increased dietary calories, increased Fe and Ca intake; increased personal hygiene and personal protective equipment (PPE); change work clothes (“foul nest” syndrome); increased ventilation and dust reduction.
- Remediation: Home lead-paint abatement, relocation, dust control, landscaping, soil removal and replacement.

Chelation Therapy

- Succimer: Administered orally, safest.
- CaNa₂EDTA: Administered IV, combine with succimer.
- BAL: Administered IM first; then add EDTA to avoid increased brain lead from EDTA alone.
- Penicillamine: Administered orally, not recommended except for treatment failures due to BM depression, penicillin — like anaphylactic reactions, and nephrotoxicity.

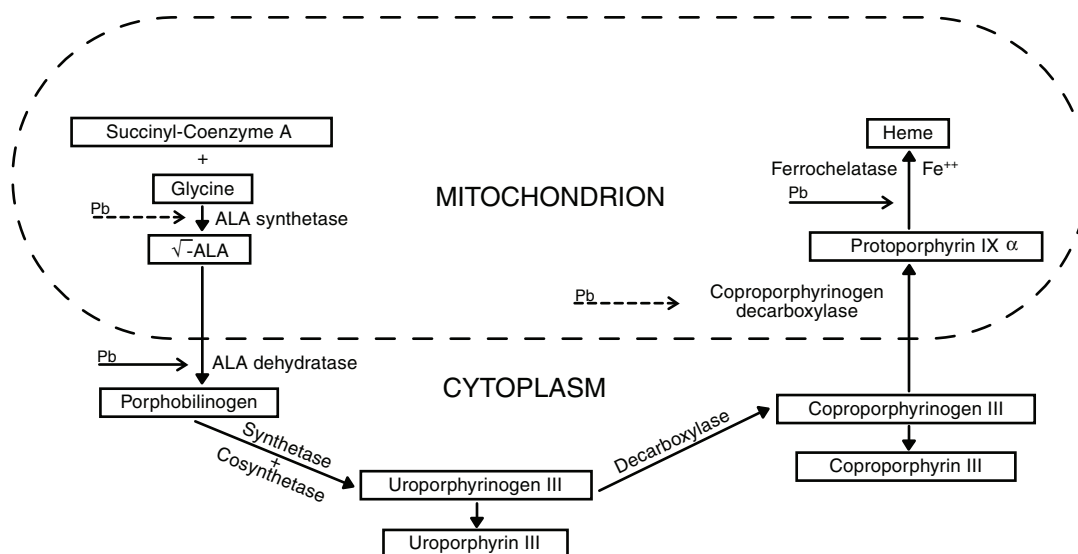


FIGURE 21.5 Mechanism of Anemia in organic lead poisoning.



FIGURE 21.6 Metaphyseal lead lines.

Chelating Agents

- BAL (British anti-Lewisite, dimercaprol): IM only, developed in World War II as antidote for Lewisite (arsine) and mustard gases; sulfur donor and nonspecific chelator of Pb, As, Cu. Side effects — hemolysis in G-6-PD deficiency, nephrotoxic in acid urine, peanut allergy; give prior to EDTA for lead encephalopathy.
- CaNa_2EDTA (calcium disodium ethylenediamine tetraacetic acid): IV > IM, water-soluble nonspecific chelator of Pb, Hg, Cu, Zn. Side effects — nephrotoxic with oliguria, IM — subcutaneous calcinosis, transient increased ALT/AST, redistribution of Pb from stomach to brain in encephalopathy.
- Penicillamine: IV > orally, nonspecific chelator of Pb, As, Hg, Cu, Zn. Side effects — aplastic anemia, nephrotoxic, teratogenic, immunosuppression, penicillin-like allergy.

- Succimer (dimercaptosuccinic acid): Administered orally only, water-soluble specific and least toxic chelator for Pb, As, Hg; will not chelate the essential minerals (Fe, Cu, Zn, Ca) and can be given with Fe supplementation; minor, mostly gastrointestinal side effects, transient increased AST.

Chelation Therapy

Adult Chelation Therapy

- Encephalopathic: BAL IM first, followed by EDTA IV.
- BPb > 100 mcg/dL: Same.
- BPb > 70–100 mcg/dL: Succimer orally only.
- BPb < 70 mcg/dL: Reduce exposure, no treatment indicated — chelation contraindicated secondary to increased BPb levels from mobilized bone stores.

Pediatric Chelation Therapy

- Encephalopathic: BAL IM first, followed by EDTA (IV).
- BPb > 70 mcg/dL: Same.
- BPb > 45–69 mcg/dL: Succimer > EDTA.
- BPb 35–44 mcg/dL: Succimer if <2 years old.
- BPb 20–44, if >2 years old: Reduce exposures, no chelation.
- BPb < 20 mcg/dL: Reduce exposures, no chelation.

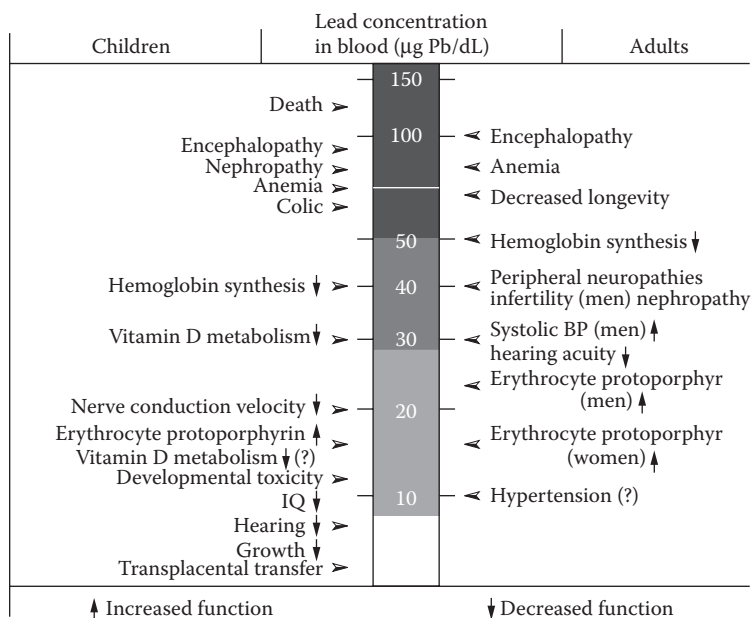


FIGURE 21.7 Correlation of clinical findings with increasing blood lead levels.

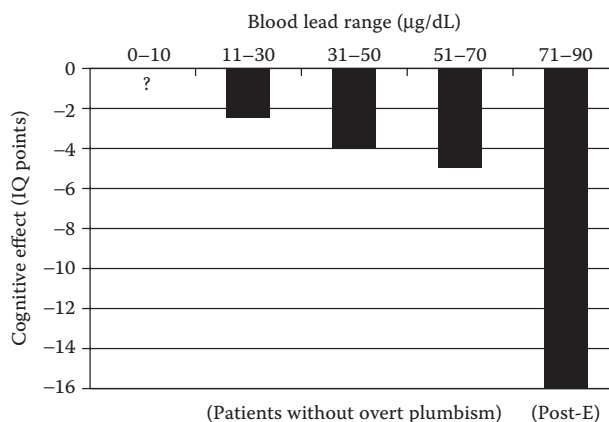


FIGURE 21.8 Correlation of increasing blood levels with decreasing IQ pts on child.

Mercury (Hg)

Forms and Exposures of Mercury

TABLE 21.4 Forms and Exposures of Mercury

Elemental Mercury	Inorganic Mercury	Organic Mercury
EX: "Quicksilver"	Mercuric chloride	Methyl mercury
Dentists	Antiseptics	Seafood, especially predatory fish
Calibrated instruments (blood pressure gauges, thermometers)	Disinfectants — taxidermy	Grain and seed fumigants
Nasogastric tubes	Batteries	Insecticides
Jewelers	Explosives	Fungicides
Electroplaters	Plastics (PVC)	Wood preservatives

Toxicology

TABLE 21.5 Mercury Toxicology

	Elemental Mercury	Inorganic Mercury	Organic Mercury
Route	Inhalation	Ingestion (gastrointestinal) > dermal (skin)	Predominantly gastrointestinal
Distribution	Lungs, CNS, kidney	CNS > kidney > gastrointestinal	CNS > fetus > kidney > liver
Excretion	Renal > gastrointestinal	Renal > gastrointestinal	Methyl: gastrointestinal — fecal Aryl: renal

Pathophysiology

- Avid covalent binding to all sulfur-containing groups, especially the sulfhydryl groups, throughout the body.
- Widespread destruction of membranes and structural proteins (CNS) and disruption of enzyme and transport systems.
- Elemental Hg targets lungs (chemical pneumonitis, ARDS), inorganic Hg targets gastrointestinal tract and kidneys (hemorrhagic gastroenteritis, ATN), organic Hg targets CNS, especially fetal CNS (Minimata disease).

- Pulmonary: Cough, chills, fever, dyspnea, chemical pneumonitis, pulmonary edema, ARDS, interstitial fibrosis.
- Gastrointestinal: Metallic taste, nausea, vomiting, diarrhea, dysphagia.
- CNS: Headaches, weakness, visual disturbances.

Acute Inorganic Ingestion

- Gastrointestinal > renal effects:
 - Gastrointestinal: Metallic taste, oral pain and burning, nausea, vomiting, diarrhea, abdominal pain, hemorrhagic gastroenteritis, dehydration → orthostatic hypotension.
 - Renal: Proximal tubular necrosis → ATN.

Clinical Syndromes

Mercury Acute Clinical Effects

Acute Elemental Inhalation

- Pulmonary > gastrointestinal > CNS effects:

Mercury Chronic Clinical Effects

Elemental Mercury

- Pulmonary > renal > gastrointestinal effects:

- Pulmonary: Pulmonary fibrosis, restrictive lung disease.
- Renal: Fanconi's syndrome = proteinuria → nephrotic syndrome follows autoimmune glomerulonephritis, high case fatality rates.
- Gastrointestinal: Relatively nontoxic due to negligible absorption (e.g., after long-naso-gastric tube balloon rupture).

Inorganic Mercury ("mad hatter" syndrome)

- CNS > renal > gastrointestinal effects:
 - CNS: Intention tremor, ballismus and choreoathetosis ("mad hatter" syndrome), erethism (anxiety, emotional lability, memory loss), neurasthenia (headache, depression, fatigue anorexia, weight loss).
 - Renal: ATN 1–2 weeks following ingestion.
 - Gastrointestinal: Metallic taste and a characteristic triad of inorganic mercury poisoning: (1) gingivostomatitis, (2) loose teeth, and (3) salivary gland hyperplasia.

Methyl Mercury Poisoning and Acrodynia

Methyl Mercury Poisoning

- Toxic form: Inorganic Hg transformed by marine bacteria to organic methyl Hg — bio-concentrated up the seafood chain.
- Common name: Minimata disease.
- Symptoms: Spontaneous abortions, fetal neurotoxicity, decreased fetal birth weight, mental retardation—developmental delay, ataxia, seizures hypotonia/spasticity, deafness—blindness.

Acrodynia

- Toxic form: Inorganic Hg salts — *Calomel* and similar inorganic Hg-containing creams used for infant eczema and as inorganic mercurial teething powders in the 1950s.
- Common name: Pink disease.
- Symptoms: Pink papular distal rash with pinkish-purple acrocyanosis that may be followed by hyperkeratoses on palms and soles, with later acral desquamation and possibly ulceration.

Diagnosis and Management

TABLE 21.6 Mercury Diagnosis and Management

	Diagnosis	Emergency Management	Specific Treatment
Elemental	Urine Hg > blood Hg	Absorption, decontamination, no vacuuming, contact haz mat — 911, personal protective equipment	IM BAL and oral succimer > penicillamine
Inorganic	Urine	Esophagogastroduodenoscopy, WBI (PEG) for residual	Same as elemental
Methyl Mercury	Blood Hg	N/A	Treatment resistance, succimer

Thallium (Th)

Properties of Thallium

- Soft, pliable toxic metal.
- Common component of granite and shale.
- Behaves like K^+ ion in the body, interfering with nerve conduction, especially in the longest peripheral nerves and may lead to painful, glove-and-stocking neuropathy.

Metabolism/Excretion

- Not metabolized.
- Does not persist in tissue storage sites, like Pb and Cd in bone.
- Gastrointestinal–fecal excretion (50+%), unlike most other heavy metals > renal–urine excretion (25+%) > sweat, hair, nails (<10%).

Uses and Exposures of Thallium

- Alloys and anticorrosives
- Optical lenses
- Coatings for lamp and lantern filaments (Coleman lanterns)
- Jewelry
- Depilatories
- Rodenticide — outside United States
- Radioactive contrast agent: Thallium cardiac scans for noninvasive measurement of cardiac ejection fraction (EF) (“dirty bomb” component)

Toxicology

Absorption/Distribution

- Rapidly absorbed by all routes.
- Inhalation and ingestion > dermal absorption.
- Distributed rapidly throughout the body.
- Partitions into a three-compartment model: (1) blood, (2) well-perfused organs, (3) CNS, no storage in reservoirs, like Pb and Cd.

Pathophysiology

- Thallium ions preferentially accumulate in all areas of high K concentration, particularly central and peripheral nerves, liver, and muscle, including cardiac muscle.
- Thallium replaces K in all K-dependent enzyme systems.
- Thallium impairs nerve conduction and muscle membrane depolarization: sensory > motor, long nerves (lower extremity) > short nerves (upper extremity).
- Thallium decreases mitotic activity (causing total alopecia) and combines with sulfhydryl groups, like arsenic, weakening keratin in nails → causing Mees’ lines on fingernails and to a lesser extent, toenails.
- Exception: Unlike other heavy metal salts, thallium salts are substantially adsorbed to activated charcoal.

TABLE 21.7 Thallium Clinical Effects

Immediate	Intermediate	Late	Chronic
3–4 hours	Hours to days	2–4 weeks	Months
No. 1 = gastrointestinal	No. 1 = PNS	No. 1 = dermal	No. 1 = CNS
Nausea, vomiting, cramps, constipation (vagal neuropathy)	Painful ascending peripheral neuropathy, cranial nerve palsies	Alopecia, Mees’ lines	Optic neuritis, ophthalmoplegia
Autonomic (X) neuropathy	Alopecia	Motor neuropathy	Memory and cognitive loss

TABLE 21.8 Thallium Diagnosis and Treatment

Diagnosis	Early Management	Late Treatment
24-hour urine for atomic absorption spectroscopy	Lavage > emesis if no vomiting, whole-bowel irrigation if x-ray is positive	MDAC and mannitol (osmotic cathartics only)
Urine > blood > hair and nails Thallium levels	Prussian blue chelation	Prussian blue = K ferric ferrocyanide
Abdominal x-ray for radiopaque gastrointestinal sludge — whole-bowel irrigation — with polyethylene glycol (PEG) solutions if positive	MDAC and cathartic, mannitol > sorbitol due to reduced GI motility	Prussian blue exchanges its K for thallium and cesium ions during chelation

Differential Diagnosis: Alopecia and Mees Lines

Differential Diagnosis of Total Alopecia

- Thallium
- Arsenic
- Selenium
- Colchicine
- Vinca alkaloids

Differential Diagnosis of Mees Lines

- Thallium
- Arsenic
- Mitotic inhibitors: colchicine, dapsone
- Antimetabolites

Minor Metal Toxicity

Nickel

Nickel Uses and Exposures

- Steel and other alloys
- Nickel–cadmium batteries
- Electroplating
- Cooking utensils: pots and pans
- Coins
- Ceramic glazes
- Green glass
- Jewelry

Acute Nickel Toxicity

- Toxicity: Gastrointestinal > Pulmonary:
 - Gastrointestinal: Nausea, vomiting, diarrhea, abdominal cramps, hemorrhagic gastritis.
 - Pulmonary: Dyspnea, chest pain, rhinitis, sinusitis, tracheobronchitis/croup; targets upper airway like Cr.
 - Dermal: Allergic > irritant contact dermatitis.
 - Eye: Conjunctivitis.

Chronic Nickel Toxicity

- No. 1 = bronchopulmonary.
- Upper airway: Anosmia, nasal polyposis, nasal septal perforation, chronic bronchitis, nasal cancer; similar to chromium — “chrome holes” and nasal septal perforation.
- Lower airway: Chronic bronchitis, pulmonary fibrosis, lung cancer.

Treatment: Nickel Poisoning

- Remove from the source.
- Specific chelation therapy only with dithiocarb, a disulfiram metabolite that binds nickel and also platinum (platinoid cancer chemotherapeutics).
- Topical dithiocarb can be used to manage nickel and platinum allergic contact dermatitis.

Differential Diagnosis of Garlic Breath

- Garlic consumption
- Selenium, selenious acid
- Dimethyl sulfoxide (DMSO)
- Phosphorous, zinc phosphide (rotten fish)
- Arsenic
- Tellurium

Cobalt

TABLE 21.9 Cobalt

Exposures	Acute Toxicity	Chronic Toxicity	Treatment
Grinders, polishers	Irritant dermatitis	Polycythemia	Remove from source
Machinists, tool sharpeners	Allergic dermatitis	Cardiomyopathy	Decontamination
Beer from stabilizers (Canada)	Occupational asthma	Hypothyroidism, pulmonary fibrosis	Chelation with CaNa_2EDTA

Copper

TABLE 21.10 Copper

Exposures	Acute Toxicity	Chronic Toxicity	Treatment
Alloys, electrical wiring	Gastrointestinal: metallic taste, nausea, vomiting, diarrhea, gastrointestinal bleeding, jaundice	Pulmonary fibrosis, lung cancer, Wilson's disease	Lavage, catharsis, chelation for Wilson's disease
Algicides, fungicides	Metal fume fever, hemolysis	Decreased ceruloplasmin, blindness, cirrhosis	Chelation — d-penicillamine only
Preservatives, pigments	Irritant > allergic dermatitis	Encephalopathy	Liver transplantation (Wilson's)

Manganese

TABLE 21.11 Manganese

Exposures	Acute Toxicity	Chronic Toxicity	Treatment
Alloys, welding, solders	MgO_2 — acute pneumonitis (manganic pneumonia)	Parkinsonism — reduced dopamine levels uniquely in: Corpus striatum and glorus pallidus	Early chelation only
Animal food additives	Conjunctivitis, dermatitis		CaNa_2EDTA
Fertilizers	Gastrointestinal — caustic mucosal and orogastric burns	Intention tremor, dystonia, pulmonary fibrosis	L-dopa for Parkinson's disease

Selenium

TABLE 21.12 Selenium

Exposures	Acute Toxicity	Chronic Toxicity	Treatment
Gun bluing solvents	Gastrointestinal: garlic breath, nausea, vomiting, watery diarrhea	Gastrointestinal distress, garlic breath, metal taste	Chelation contraindicated, secondary nephrotoxicity
Alloys	Abdominal cramps	Anosomnia, reactive airways dysfunction	Activated charcoal
Antifungal shampoos (Selsun Blue®)	Caustic burns, dry hair, paresthesias	Antioxidant and possible anticancer effects, possibly reduces prostate cancer risks	Add a cathartic

Tin

TABLE 21.13 Tin

Exposures	Acute Toxicity	Chronic Toxicity	Treatment
Alloys — bronzes, solders, electroplating	Benign pneumoconiosis =	Peripheral demyelinating neuropathy (organotin)	Chelation with BAL
Cooking utensils	Stannosis	Encephalopathy	No. 1 — BAL
Toothpastes, algicides, fungicides		Cerebral edema	BAL > DMSA

Zinc

TABLE 21.14 Zinc

Exposures	Acute Toxicity	Chronic Toxicity	Treatment
Alloys, brasses, bronzes, welding, solders	Metal fume fever, contact dermatitis	Copper deficiency — sideroblastic anemia, bone marrow depression	Remove from source
Galvanized pipes	Abdominal cramps	Leukopenia	Replace copper with oral mineral supplements
Electroplating	Diarrhea	White cell aplasia	

Industrial Gas Exposures

Chapter Outline

Simple asphyxiants

- Definitions
- Noble gases
- Hydrocarbon (HC) gases
- Physiologic asphyxiants

Pulmonary irritants

- Irritant gases
- Irritant gas exposures: ALI vs. RADS
- Irritant gas toxic mechanisms

Smoke inhalation

- Epidemiology
- Pathophysiology
- Management

Carbon monoxide (CO) poisoning

- Epidemiology
- Pathophysiology
- Delayed effects
- Diagnosis and treatment

Cyanide poisoning

- Exposures and settings
- Mechanisms of toxicity
- Clinical manifestations
- Management

Hydrogen sulfide (H₂S) poisoning

- H₂S exposures and settings for poisoning
- Mechanisms of toxicity
- Clinical manifestations
- Management

Simple Asphyxiants

Definitions

- Nonirritating, colorless, and odorless gases with no pharmacologic or physiologic (except: $\text{CO}_2 > \text{N}_2$) activities. All are easily compressible and expand logarithmically on rapid depressurization.
- Produce hypoxic tissue damage, mainly to the brain and myocardium, by displacing alveolar O_2 .
- Treatment includes evacuation, supplemental O_2 , ventilatory assistance, and support. Hyperbaric oxygenation (HBO) is not indicated unless there is co-exposure to CO or H_2S .

Noble Gases

- Helium: Used to dilute O_2 in deep-sea diving; used as a carrier gas to bypass bronchoconstriction in asthmatics, and used as the inflating gas for intraaortic balloon pump (IABP). Helium is well suited for these uses because of its compressibility, nonflammability, low density, low viscosity, and low lipid (tissue) solubility.
- Argon and neon: Lighting manufacture.
- Xenon: General anesthetic at 1 atm.
- Radon: Alpha-particle emitter and carcinogen.

Hydrocarbon (HC) Gases

- Methane: “Swamp gas” used as fuel for cooking, clothes drying, driving autos, and generating electrical power.
- Ethane: A natural gas component used as a refrigerant.
- Propane: A compressed gas fuel and liquid solvent.
- Butane: A cigarette lighter and fire-starter fuel and liquid solvent. Often abused by inhalation (“huffing”).

Physiologic Asphyxiants

Carbon Dioxide

- Uses: Carbonating beverages, fire fighting, solid “dry ice,” formerly laparoscopic insufflation (CO_2 ’s high solubility can promote rapid absorption cause metabolic and respiratory acidosis during laparoscopic surgery; replaced by insoluble nitrous oxide as insufflating gas for laparoscopy).
- Toxicity: Respiratory acidosis from carbonic acid accumulation, compensatory respiratory alkalosis, arrhythmias from acidosis and hypokalemia

Nitrogen

- Uses: Fertilizer, cryosurgery (liquid N_2), compressed gas for power tools.
- Toxicity: Nitrogen narcosis (“rapture of the deep”); use helium > air with 80% N_2 as the preferred diluent gases for O_2 in deep-sea diving operations; and ascend slowly and incrementally to prevent N_2 bubble decompression and resulting CNS narcosis, abdominal pain (“bends”), and long bone (femoral heads) and vertebral osteonecrosis.

Pulmonary Irritants

- Impact of increasing water solubility on irritant gas toxicity
- Outcomes of irritant gas poisoning: Acute lung injury (ALI) vs. reactive airways dysfunction syndrome (RADS)
- Pathophysiology of irritant gas toxicity
- Caustic (acid-base) effects of irritant gases
- “Tear gases” = irritant gases with high toxicity, and “knock-down” human effects with increased morbidity, but reduced mortality. The search for “kinder and gentler” tear gases = capsaicin (pepper spray)

Irritant Gases

High Water Solubility

- Ammonia (NH_3)
- Chloramines
- Hydrogen chloride (HCl)
- Hydrogen fluoride (HF)
- Sulfur dioxide (SO_2)
- Acrolein
- “Tear gases”

Intermediate Water Solubility

- Chloride/chlorine (Cl_2)
- Methylisocyanate (MIC) (Bhopal, no cyanide (CN) poisoning)
- Immune diisocyanate (DI) sensitizers:
 - Toluene diisocyanate (TDI)
 - Diphenylmethane diisocyanate (MDI)

Low Water Solubility

- Phosgene
- Ozone

Metal Fume Fevers

- Zinc and Copper — most common causes.
- Cadmium — acute pneumonitis > metal fume fever.

Irritant Gas Exposures: ALI vs. RADS

Acute Lung Injury (ALI)

- Pathology: Acute pulmonary inflammation and alveolar fluid filling.
- Symptoms: Dyspnea, chest tightness, chest pain, cough, frothy sputum, rales, rhonchi.
- X-ray: Pulmonary infiltrations, normal cardiac silhouette.

Reactive Airways Dysfunction Syndrome (RADS)

- Pathology: Chronic hyperreactive lower airways with asthmatic bronchospasm.
- Symptoms: Wheezing, tachypnea, air hunger, “irritant-induced asthma.”
- X-ray: Air trapping = hyperinflation, flattened hemidiaphragms, elongated cardiac silhouette, “obstructive emphysema” pattern on the chest x-ray.

TABLE 22.1 Irritant Gases

Highly Soluble	Intermediate	Poorly Soluble
Prompt escape	Less escape prompting	No escape prompting
Rapidly irritating to mucosa	Less irritating to mucosa	No mucosal irritation
Target upper airway and EENT mucosa	Target tracheobronchial tree	Target pulmonary parenchyma
Acute lung injury (ALI) possible	ALI Common	Delayed, severe pneumonitis
Reactive airways dysfunction syndrome (RADS) possible	RADS common	Pulmonary edema

Irritant Gas Toxic Mechanisms

1. Local caustic generation on tissue hydration
→ causes immediate mucosal neutralization burns:

Irritant Gases	Mucosal Caustics Produced
Ammonia	→ Ammonium hydroxide
Chloramines	→ Hypochlorous acid
Hydrogen chloride	→ Hydrochloric acid
Hydrogen fluoride	→ Hydrofluoric acid
Hydrogen sulfide	→ Cytochrome oxidase inhibition, lactic acid (metabolic acidosis)
Sulfur dioxide	→ Sulfuric acid
Chlorine	→ Hypochlorous and hydrochloric acids

2. Free radical generation on lung tissue absorption
→ causes pulmonary parenchymal damage:

Irritant Gases	Free Radicals Generated
Oxygen	→ Superoxide and singlet O radicals
Oxides of nitrogen (NOx)	→ NO, NO ₂ , N ₂ O, and N ₂ O ₃ , all generate peroxynitrite free radicals; NOx also dissolve in lung water generating nitric and nitrous acids, causing further caustic burn injury to pulmonary parenchyma
Ozone – generated by air	→ Superoxide and singlet O free radicals pollution, lightning, and electrical fires, welding

TABLE 22.2 Caustic Irritants

Gas	Exposure	Toxicity
NH ₃	Fertilizer/explosives, cleansers	Reactive airways dysfunction syndrome (RADS)
Chloramines	Water treatment	ALI, RADS
Hydrogen chloride (HCl)	PVC	RADS
Hydrogen fluoride (HF)	Rust removal	Reduced Ca/Mg (treatment: Ca glue)
Hydrogen sulfide (H ₂ S)	Oil refinery, sewage	Cytochrome poison (treatment: consider HBO)
Sulfur dioxide (SO ₂)	Autos, smog, acid rain	RADS
Chloride (Cl)	Water treatment	ALI (consider nebulized NaHCO ₃)
Acrolein	Polypropylene	Pulmonary edema

TABLE 22.3 Tear Gases

Aerosol ("gas")	Mechanism	Toxicity
Chloroacetophenone (CN), mace	Highly water soluble irritant	Tearing, eye pain, dermal burns, cough, RADS
Chlorobenzylidene malononitrile (CS)	Same	Same
Capsaicin pepper spray = kinder gentler tear gas	Peripheral pain c-fibers release substance P causing neurogenic inflammation	Less oculotoxic, pulmonary edema, bronchospasm, possible RADS

Smoke Inhalation

Epidemiology

- There are 3600 fire-related deaths and nearly 30,000 fire-related injuries/year in the United States.
- 50–80% of the fire deaths are due to smoke inhalation.
- The United States has the highest fire death rates in the world.
- Pyrolysis of wood produces nearly 200 toxic combustion products. Pyrolysis of PVC-containing plastics and fabrics produces at least 75 toxic combustion products, including cyanide.

Pathophysiology

Pathology and Outcome

- CNS toxicity: Hypoventilation, asphyxia, coma.
- Airway edema: Stridor, dyspnea, chemical tracheobronchitis, croupy cough.
- Airway obstruction: Cough/wheeze bronchospasm, hypoxemia.
- Atelectasis: Rales, respiratory failure; first x-ray changes = pulmonary edema, pneumonia, atelectasis.

- Impaired O₂ transport from CO, CN, and H₂S poisoning with neurologic depression, hypoventilation, respiratory acidosis, and metabolic acidosis triggering hypoperfusion, arrhythmias, angina.
- Impaired tissue oxygenation (from CO, CN, H₂S poisoning) and hypoperfusion.

Management

- O₂, airway support, “coma cocktail” for unconsciousness = naloxone, dextrose, and thiamine
- O₂, endotracheal intubation
- O₂, bronchoscopy to remove soot and reactive “diphtheritic” endobronchial membranes, β_2 -agonists to reverse bronchospasm
- O₂, mechanical ventilation: CPAP, IMV, PEEP
- O₂, HBO, methylene blue (for methemoglobin levels > 20-30%)
- O₂, vasopressors, HBO for CO poisoning (COHb levels > 25%), cyanide kit for CN poisoning

Carbon Monoxide (CO) Poisoning

Epidemiology

- CO is the leading cause of poisoning morbidity and mortality in the United States, causing >5000 deaths/year.
- 50+% of the CO deaths/year are caused by auto exhausts; 500 CO deaths/year are caused by non-autos, such as stoves, fireplaces, gas heaters, electrical generators, propane-powered indoor equipment (forklifts and Zamboni® ice resurfacers).
- 3–24% of symptomatic patients with flu-like symptoms of headache, nausea, lethargy, and dizziness reporting to EDs/year have CO poisoning.
- CO is the most common cause of fire deaths; smokers can have COHb levels of 6–10%, increasing their susceptibility to CO poisoning.
- 14–40% of discharged patients treated for CO poisoning will have delayed, permanent neurologic dysfunction, such as parkinsonism.
- In addition to combustion of fossil fuels (oil, gas, coal, wood) and cigarette smoking, methylene chloride-containing paint strippers are the next highest contributors to human carboxyhemoglobin (COHb) levels. Methylene chloride is rapidly absorbed through the skin and lungs and converted to CO by the liver.

Pathophysiology

- Hemoglobin (Hb) binds to CO with an affinity 250× greater than for O₂ binding.
- CO shifts the oxyHb dissociation curve leftward, decreasing oxygen unloading to tissues, causing tissue hypoxia and lactic acidosis.
- CO also binds to myoglobin, impairing myocardial performance and causing myonecrosis and myoglobinuria.
- CO can displace NO from platelets, causing peripheral vasodilation and hypotension.
- CO may interfere with cellular respiration by binding to mitochondrial cytochrome oxidase, like cyanide (CN), uncoupling oxidative phosphorylation, and contributing to tissue hypoxia and lactic and metabolic acidosis.

Delayed Effects

- Patients rendered unconscious, pregnant, or over 30 years old during CO exposure are more susceptible to delayed, often permanent, neurologic effects of CO poisoning, referred to as the carbon monoxide–delayed neuropsychiatric syndrome (CO-DNS).
- Delayed neurologic effects = amnesia, agnosia, apraxia, dementia, incontinence, psychosis, chorea, cortical blindness, peripheral neuropathy, parkinsonism.

TABLE 22.4 Carbon Monoxide: Clinical Manifestations

Severity: % COHb	Symptoms	Signs
Mild: 5–15%	Headache, nausea, lethargy, dizziness	Vomiting, no sequelae
Moderate: 15–25%	Obtundation, weakness, chest tightness, dyspnea	Tachycardia, angina, tachypnea, ataxia, myonecrosis
Severe: >25%	Chest pain, palpitations, disorientation, loss of consciousness	Tachyarrhythmias (PVCs), myocardial infarction (MI), hypotension, seizures, coma, skin bullae, cherry-red skin color, permanent CNS damage (parkinsonism), death

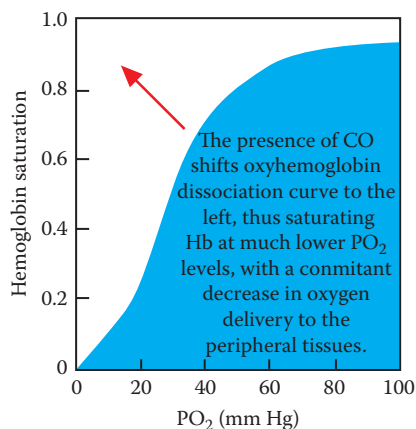


FIGURE 22.1 The presence of carbon monoxide (CO) in the blood following its inhalation will shift the orientation of the oxyhemoglobin dissociation curve leftward, causing hemoglobin to become saturated at lower oxygen tension levels (PO_2) and delivering less oxygen to the organs and tissues.

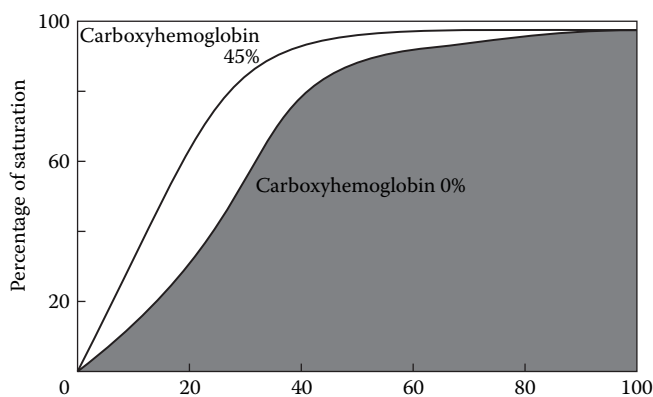


FIGURE 22.2 The presence of carbon monoxide (CO) in the blood following its inhalation will shift the orientation of the oxyhemoglobin dissociation curve leftward, causing hemoglobin to become saturated at lower oxygen tension levels (PO_2), and delivering less oxygen to the organs and tissues. This diagram depicts a comparison of a normal oxyhemoglobin dissociation curve and an abnormal oxyhemoglobin dissociation curve shifted leftward by 45% carboxyhemoglobin in the blood.

- Delayed neurologic sequelae can be predicted from acute changes on CT and MRI scans, especially basal ganglia lesions (globus pallidus) and ischemia of subcortical white matter.

Diagnosis and Treatment

Lab Diagnosis

- COHb level monitoring by co-oximetry only.
- ABGs (normal PaO_2 maintained) and pulse oximetry (COHb maintains normal O_2 saturation) are both very unreliable and underestimate extent of tissue hypoxia in CO poisoning.
- ABGs to confirm lactic and metabolic acidosis.
- Mildly elevated CPK from myonecrosis.

Indications for Hyperbaric Oxygenation (HBO)

- Immediate HBO:
 - COHb > 25% by co-oximetry
 - COHb > 15% in pregnancy
- Any local CNS findings: Syncope, seizures, coma, lateralizing neurologic signs.
- ECG: Myocardial ischemia, PVCs/any tachydysrhythmias.
- HBO after initial treatment (100% O_2 required every 2–4 hours): Persistent neurologic findings = headache, dizziness, confusion, and ataxia.

Cyanide Poisoning

Exposures and Settings

Cyanide Exposures

- Suicides/homicides involving chemists and lab workers.
- Consumer product tampering.
- Residential fires involving fabrics and synthetics: synthetic rubber, wool, silk, polyurethane, nitrocellulose in curtains and furniture upholstery.
- Ingestion of acetonitrile-based nail polish removers.
- Plants: (1) *Prunus* spp. pitted fruits = apricots, apples, cherries, peaches, almonds; (2) hydrangeas → gut-transformed to amygdalin → HCN.
- Iatrogenic sodium nitroprusside (SCN) infusions.

Clinical Settings for Cyanide Toxicity

- Sudden collapse of an academic or industrial lab or chemical worker.
- Fire victims with coma and metabolic acidosis.
- Suicide or unexplained coma and acidosis.
- Ingestion of or access to artificial nail polish remover.
- Cancer patients on “Laetrile®” (amygdalin or cyanide-containing “anticancer” hoax) treatment.
- ICU patients on prolonged SCN⁻ infusions.

Mechanisms of Toxicity

- Rapid absorption via all routes with rapid membrane transit promoted by cyanide’s limited ionization and low molecular weight.
- Initial inhibition of cytochrome oxidase, shutting down electron transport chain, blocking aerobic ATP-energy production in mitochondria, and causing cellular hypoxia.

- Stimulation of alternative anaerobic routes of ATP-energy production from pyruvate with lactate production, lactic and metabolic acidosis.
- Direct CNS neurotoxicity through lipid peroxidation and ischemia with greatest damage to the most O₂-sensitive areas of the brain in the basal ganglia.

Clinical Manifestations

Acute Manifestations

- Unique: Bitter almond breath and body odor detectable by only 40% of the population.
- CNS: Predominant progressive symptoms of anxiety, agitation, confusion, lethargy, seizures, coma, central tachypnea progressing to agonal bradypnea.
- Cardiovascular: Initial bradycardia and hypertension, then tachycardia and hypotension, then myocardial failure.
- Skin: Cherry-red skin color progressing to agonal cyanosis.

Delayed Manifestations

- CNS neurotoxicity predominates: Confined to basal ganglia = globus pallidus, putamen, hippocampus (CT confirmation) resulting in toxic parkinsonism, with bradykinesia, dystonia, dysarthria, no rigidity (L-dopa resistant).
- Chronic low-level cyanide toxicity occurs in: (1) Tobacco amblyopia (male smokers); (2) tropical (cassava root) ataxic neuropathy, (3) Leber’s hereditary optic atrophy (males). Mechanism: low endogenous stores of CN-detoxifying hydroxocobalamin and thiosulfate. Results from depletion of detoxifying substances by chronic low-grade CN poisoning from cigarette smoking (tobacco amblyopia and Leber’s hereditary optic atrophy) or frequent cassava root ingestion (tropical ataxic neuropathy).

Management

Lab Diagnosis

- Assess for metabolic acidosis with ABGs, central venous gas, serum lactate, glucose, electrolytes, renal function tests — BUN, creatinine.
- Request serum and gastric aspirate cyanide levels.
- Obtain baseline ECG.
- Monitor with co-oximetry for methemoglobin (metHb) and cyanmethemoglobin (cyanmetHb) after nitrite administration (first by amyl nitrite inhalation, then by intravenous sodium nitrite).

Treatment

- Decontamination: Lavage + 1 g/kg AC, remove all contaminated clothes and wash skin.
- Antidote: Cyanide kit = (1) amyl nitrite insufflation and/or (2) IV 3% sodium nitrite, 10 mL over 30 min, (3) IV 25% sodium thiosulfate, 50 mL.
- Additional treatment: The B_{12} precursor, hydroxocobalamin, may be used to displace CN from cytochrome oxidase and form non-toxic cyanocobalamin (vitamin B_{12}) to be further metabolized to nontoxic metabolites by the rhodanase–thiosulfate pathway.

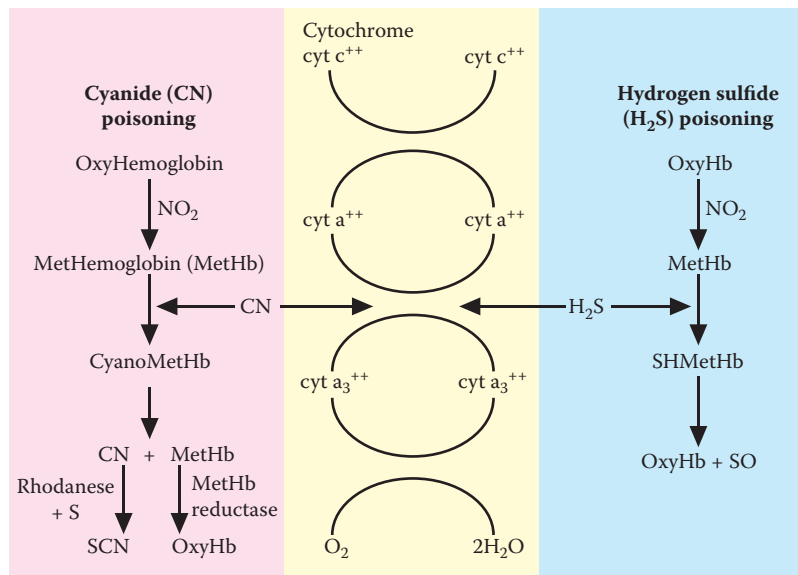


FIGURE 22.3 The shared toxicities and similarities in treatment strategies for cyanide or hydrogen cyanide gas poisonings. The shared impact of cyanide (CN) or hydrogen sulfide (H₂S) gas poisoning on the cytochrome oxidase electron transport system and the oxygenation of hemoglobin. This diagram also depicts the rationale for inducing methemoglobinemia with nitrites in the detoxification of both CN and H₂S poisoned patients.

Hydrogen Sulfide (H₂S) Poisoning

Sources and Mechanisms

Sources of Exposures

- Natural gas: Bacterial decomposition of proteins, including vegetation, human sewage, animal remains and wastes, and decaying fish, creates marsh-swamp gases = methane and H₂S.
- Natural events: Volcanoes, sulfur springs, natural gas fields, marine vent tube worms.
- Industrial: Paper mills, oil/gas refineries, leather tanning and manufacture.

Toxic Pathophysiology

- Rapid absorption via lungs and easy membrane transit due to the high lipid solubility of H₂S.
- H₂S, like CN, inhibits cytochrome oxidase (aa₃) uncoupling oxidative phosphorylation and limiting ATP-energy production.
- H₂S binds to endogenous metHb to form sulfmethemoglobin (sulfmetHb) with even greater

affinity than it binds to mitochondrial cytochrome oxidase.

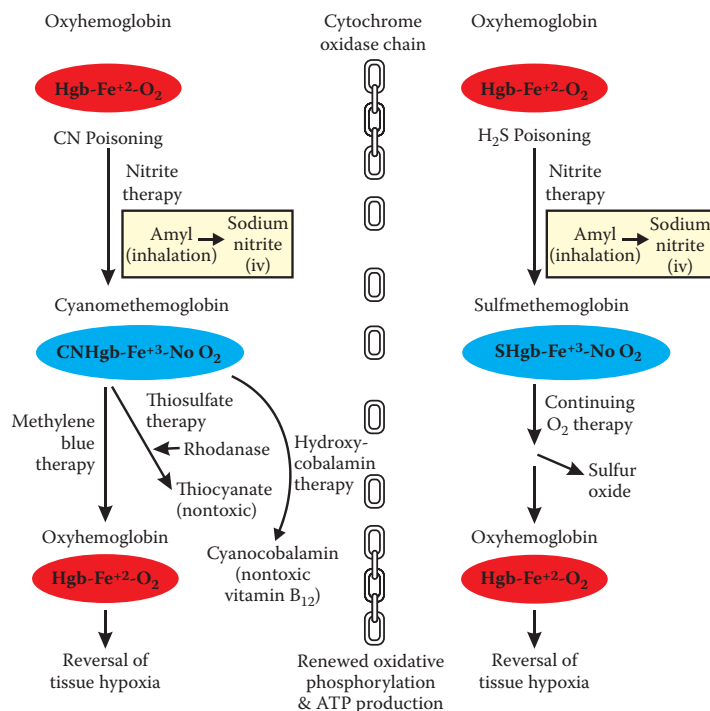
- H₂S causes K-channel-mediated neuronal hyperpolarization and potentiates neuronal inhibition.

Clinical Manifestations

Suspect Hydrogen Sulfide Poisoning

- Rapid “knock-down” effect.
- Rapid loss of consciousness.
- Blackening and/or darkening of pocket change and any jewelry items — watch, necklace, etc.
- Breath and body odor smell of rotten eggs.
- Low odor threshold: 0.02–0.13 ppm.
- Mucosal irritation: 50–150 ppm.
- Rapid olfactory fatigue and paralysis: 100–150 ppm, smell no longer appreciated.

FIGURE 22.4 The pathophysiology and management of cyanide or hydrogen sulfide gas poisoning. Restoring the disrupted cytochrome oxidase chain in cyanide and hydrogen sulfide gas poisoning with specific and shared treatment strategies.



Confirm Clinical Suspicion

- HEENT: Severe mucosal irritation and edema; keratoconjunctivitis can lead to corneal epithelial ulcers (“gas eye”); rhinitis.
- Cardiovascular: Bradycardia, angina.
- Pulmonary: Dyspnea, cyanosis, bronchitis, cough, hemoptysis, pulmonary edema.
- Gastrointestinal: Nonspecific nausea and vomiting.
- CNS: Headache, weakness, dysequilibrium, seizures, coma.

Treatment

- Prehospital: Evacuate with self-contained breathing apparatus, provide high-flow oxygen, provide best airway and support ventilation.
- Hospital: Manage acidosis and provide inotropic support.
- Antidote: (1) 3% sodium nitrite, 10 mL IV over 15 minutes, to induce metHb, then sulfmetHb; (2) HBO if immediately available.

Management

Lab Diagnosis

- Assess for metabolic acidosis with arterial blood gases (ABGs) and elevated serum lactate levels.
- Monitor metHb levels with co-oximetry.
- MRI: To assess delayed and often permanent neuropsychiatric sequelae secondary to subcortical white matter demyelination and globus pallidus degeneration.

Radiation Toxicology

Chapter Outline

Introduction

Historical events

- Who is at risk?

Definitions

Basic science of radioactivity

Types of radiation

Units of measure

- Radiation monitoring
- Laws of radiosensitivity

Sources of radiation exposure

Radioactive isotopes

Types of radiation exposure

Preparing for arrival of victims

Diagnosis

External contamination

Internal contamination

External irradiation

Whole body radiation/acute radiation syndrome (ARS)

- Treatment of ARS
- Local radiation exposure
- Special populations

Radiation exposures during pregnancy

- Exposure of pregnant patients
- Exposures from nuclear medicine studies
- Fetal radiation risks and health effects
- Gestational age and radiation dose
- Malformations and CNS effects from fetal exposure
- Steps to prevent exposures
- Pregnancy confirmation and evaluation
- Radiation exposure of pregnant workers

Resources for radiation emergencies

- Review NIOSH publications
- Additional resources

Introduction

- Radiation injuries and the nature of radiation itself have been studied vigorously over the past century as a result of expanding use and prevalence in our society.
- Radiation: Energy sent out in the form of waves or particles.
- There are two primary forms of radiation, known as ionizing and nonionizing radiation; these shall be covered in more detail later.
- Major radiation accidents worldwide. Human experiences, 1944 to March 1999.

Historical Events

- 1895, Wilhelm Roentgen discovered x-rays.
- 1896, Henri Becquerel discovered natural radioactivity.
- Thomas Edison conducted thousands of experiments using an x-ray generator. In 1896, he reported corneal injuries in several of his workers. His assistant Clarence Dally became the first radiation-related death in the United States.
- 1899, Ernest Rutherford discovered that uranium compounds produce three different kinds of radiation. He separated the radiations according to their penetrating abilities and named them alpha, beta, and gamma radiation, after the first three letters of the Greek alphabet.
- The British Army used portable x-ray machines to find bullets and shrapnel in wounded soldiers in Sudan.
- Emergence of radioactive substances as health products.
- 1915, British Roentgen Society, recognizing the potential hazards for radiation, proposed standards for radiation protection of workers: shields, medical exams, restricted work hours.
- 1917, United States. Radium Luminous Materials Corporation painted radium luminescent paint on watches/jewelry. Mostly female workers would use lips to point the paintbrushes. By 1927, about 100 of the women would die from osteosarcoma or brain tumors, and would develop noncancerous lesions of mouth, related to radium exposure.
- 1945, only atomic bombs used in war: Little Boy (Hiroshima, Japan) had a uranium core; the blast was equivalent to 12,500 tons of TNT. Fat Man (Nagasaki, Japan) had a plutonium core; the blast was equivalent to 20,000 tons of TNT.
- Estimates of dead: +200,000.
- Most died from the bomb blasts, but many thousands also died of acute radiation syndrome and subsequent radiation-induced cancers.
- 1950s, physicians used a thorium-containing contrast agent, Thoratrast (alpha-emitting). Found to have a very slow elimination rate, accumulated in hepatic tissue, and cases of angiosarcomas and hepatic carcinomas led to its abandonment.
- 1979, Three Mile Island, PA. No deaths or injuries, but a malfunction caused a core meltdown that was contained; led to drastic changes in nuclear power in the United States.
- 1986, Chernobyl, Ukraine. 31 acute fatalities; 116,500 exposures. Series of errors led to a fire in the number 4 reactor core, several explosions, and meltdown of the reactor. Over the first 10 days following the incident, a cloud spread to the Baltic States, Scandinavia, and Europe, carrying radioactive material (^{131}I and ^{137}Cs). Reactor entombed in a giant concrete sarcophagus. Among the 600 workers present on the site at the time of the accident, 134 received high radiation doses and suffered from acute radiation sickness. Area around Chernobyl closed in a 30 km exclusion zone.
- 1987, Goiania, Brazil. Locals scavenged the remains of an abandoned medical clinic and found a source of ^{137}Cs . Resulted in over 200 exposures and 4 deaths. It was weeks before the source of the sickness could be discovered and the proper diagnosis and treatment given.
- Since December 1990, over 50 accidents have occurred worldwide, involving more than 650 individuals. Of these, more than 250 have had significant exposure, and more than 30 have died.
- Approximately 10 million sealed sources of radiation exist in over 50 countries. Sources are encased in metal and used for medicinal, agricultural, industrial, and research purposes.
- 612 sources reported lost or stolen since 1995; 254 have not been recovered. May be more sealed sources not accounted for.

Who Is at Risk?

- Professions that may incur radiation exposure:
 - Pharmacists
 - Physicians/researchers
 - Radiologists/oncologists
 - Support staff (nurses/techs)
 - Miners: asbestos, coal, diatomaceous earth, iron, miscellaneous rare earths
 - Nuclear facility workers
 - Military
 - NASA, aerospace workers
 - Patients

Radiation Safety

- Protection is accomplished through
 1. Minimizing the time of exposure.
 2. Maximizing the distance from the source.
 3. Using a shield as appropriate.

Definitions

- **Radiation:** Energy sent out in the form of waves or particles.
- **Ionization:** The ability of high-energy radiation to displace electrons from atoms and cause matter through which it passes to become electrically charged.
- **Nonionizing radiation:** Long wavelength, low frequency, low energy form. Examples: ultraviolet rays, visible rays, infrared rays, radio waves, microwaves, lasers, ultrasound, NMR systems.
- **Ionizing radiation:** Short wavelength, high frequency, high energy forms. Emitted from unstable forms of elements called radioisotopes. Examples: x-rays and gamma rays.
- **Half-life:** Period of time it takes for a radioisotope to lose half of its radioactivity.
- **Isotope:** A variation of an element with a different number of neutrons in the nucleus. All isotopes of an element have the same number of protons; differing neutrons give isotopes of the same element different atomic weights.
- **Decay (disintegration):** Unstable isotopes spontaneously transform in order to reach a more stable configuration; may involve the release of ionizing radiation.
- **Radioisotope:** Isotope that releases ionizing radiation during its decay.
- **Criticality:** The chain reaction of fissionable atoms that results in the release of energy. Basic operating principle behind fusion bombs and nuclear reactors; an efficient means of generating energy.

Basic Science of Radioactivity

Radiation may be due to loss of alpha particles, electrons (– charged beta particles or + positrons), gamma rays, and x-rays.

- An atom can decay to a product element through the loss of a negatively or positively charged electron (beta particle or positron).
- Gamma radiation results when the nucleus releases excess energy, usually after an alpha, beta, or positron transition.

Types of Radiation

- Four main types of radiation:

1. Alpha (α): particulate
2. Beta (β): particulate
3. Neutron (N): particulate
4. Gamma (γ): nonparticulate

- Alpha (α) particles

Heavy (high mass), highly charged particle composed of two protons and two neutrons.

Travel at a low velocity and interact readily with matter

Deposit a large amount of energy in a small volume of tissue.

- Easily shielded and cannot penetrate paper. However, can penetrate epithelial tissue to a depth of 50 μm , deep enough to damage epithelium.
- Significant biologic hazard only when internalized (via inhalation, open wounds, ingestion).
- Heavy radioisotopes with an atomic number above 82 (uranium, radium, and plutonium) are sources of α particle emission.

CANNOT be detected with standard Geiger counters.

- Beta (β) particles

Smaller mass and charge, greater velocity than α particles. High-energy electrons, emitted from nuclei of unstable atoms (cesium-137 and iodine-131).

Interacts with matter to a lesser extent and creates less ionization along its path. Travels further and penetrates deeper than α .

- 8 mm into exposed skin can cause serious burns, especially if allowed to remain on skin. External coverings offer some protection.
- Note: Children more susceptible than adults due to less keratinized epithelium.
- Hazard if internally deposited.

Most radioisotopes decay by beta radiation, followed by gamma radiation.

Can be detected with routine instruments such as Geiger counters.

- Neutrons (N)

Electrically neutral particles (lack of charge prevents deep penetration); wide range of energy, velocity, and penetration power.

Unique form of exposure. High-level neutron exposure can induce radioactivity (previous stable atoms can become radioactive via neutron collision, releasing alpha and beta particles).

In human tissue, induced isotope is usually Na-24, which can be detected in urine and blood.

Sources limited to nuclear power plants, linear accelerators, and weapon assembly sites.

- Gamma (γ) radiation (and X-rays)

Electromagnetic waves (nonparticulate) with no mass or charge that travel at the speed of light.

Gamma rays are the most penetrating type of ionizing radiation, traveling many cm in tissue.

Exposure to an external source of gamma or high power x-rays represents a significant whole body radiation hazard and may result in acute radiation syndrome.

Frequently accompany alpha and beta particles, can be detected with Geiger counters and dosimeters.

Units of Measure

- Various units describe radiation dose, exposure, and quantity.

Roentgen (R) is the unit used to describe radiation exposure. Measures radioactivity per unit of air.

Rads (radiation absorbed dose) and Grays (Gy) both measure absorbed doses of radiation.

- 100 Rads = 1 Gy.
- 1 Gy = absorption of 1 joule per kilogram.

- Dose equivalent quantification:

Rems (roentgen equivalent man) or Sieverts (Sv).

- 100 rem = 1 Sv.
- Dose equivalent quantification is obtained by multiplying the dose in Rads by a quality factor that describes biologic damage.
- The quality factor for x-rays, beta particles, and gamma radiation is 1, whereas the quality factor for alpha particles and neutrons is 20.

- Quantity of radiation:

Measured by the activity or number of atomic disintegrations per unit time.

Unit is the Curie (Ci) and Becquerel (Bq).

- 1 curie = 1.37×10^{10} transformations per sec
- 1 Becquerel = 1 transformation per sec.
- 1 mCi equals 37 MBq.

Body burden is reference to internally deposited radioactive material. Different radionuclides will deliver different amounts of radiation when internalized.

Film badge measures beta, x-ray, and gamma radiation.

Dose recorded in rem or sievert.

Require processing.

Pocket dosimeters can be read by holding to light source.

- Survey meters are rate meters that record the amount of radiation detected in an area per unit of time.

Ion chambers are common survey meters for recording x-ray and gamma radiation.

Calibrated in mR/hr.

Geiger-Müller (GM) instruments used for surveys for external contamination.

Detect lower exposures of x-ray, gamma, and beta radiation.

Recorded in counts per minute (cpm): 2500 cpm \approx 1 mR/hr.

Laws of Radiosensitivity

- Three laws developed by observation of radiation damage on human tissue:

1. Radiosensitivity varies directly with the rate of cell division; rapidly dividing cells are more profoundly affected (GI tract, skin, and appendages).
2. Radiosensitivity varies directly with the number of future divisions (increased future divisions in gonads—ovaries—oogenesis; embryogenesis; testes—spermatogenesis; bone marrow—hematopoiesis; epithelial linings—gastrointestinal tract; skin and appendages [hair follicles]).
3. Radiosensitivity varies indirectly with the degree of morphological and functional differentiation (bone growth plate).

Radiation Monitoring

- Dosimeters are small devices that are worn on the upper torso and record cumulative radiation that an individual receives.

Sources of Radiation Exposure

- Average annual dose to persons in United States is approximately 3.6 mSv (360 mrem).
- Standard CXR delivers 6 to 11 mrem (0.06 to 0.11 mSv, 0.06 to 0.11 mGy).
- Barium enema, 0.7 rem (700 mrem, 7 mSv, or 7 mGy).
- Lowest dose with notable bone marrow suppression with decrease in blood counts is 10 to 50 rem (100 to 500 mSv, 0.1 to 0.5 Gy).
- Lowest total body dose from ionizing radiation in which death may be seen is in the range of 1.0 to 2.0 Gy.
- Exposure can occur by a variety of means:
 1. Background radiation
 2. Medical exposure
 3. Accidental industrial exposure
 4. Nuclear reactor accidents
 5. Detonation of nuclear weapons
- Background exposure
 - Numerous sources of background radiation.
 - Cosmic and terrestrial radiation: 60 mrem/year.
 - Natural radioactivity in body: 40 mrem/year.
 - Radon: (variable: ~200 mrem/year).
 - Radioactive noble gas enters homes/buildings from the materials themselves or cracks in the structure.
 - Risk to humans via inhalation and increased risk for lung cancer. Smokers have even more increased risk.
 - Areas of NY, NJ, PA have particularly high levels.
 - Air travel, smoke detection devices, food products, and fluorescent materials: (~10 to 20 mrem/year).
- Medical exposure
 - Radiation used extensively for diagnosis and treatment.
 - CXR, cardiac catheterization (16 rem), administration of radioactive elements (technetium, brachytherapy, and radiation therapy).
- Industrial exposure
 - Radiation used to examine high-pressure pipe welds, valves, vessels.
 - Industrial accidents account for the largest amount of radiation injuries. Include:
 1. Inadvertent discharge of radioactive waste into the environment.
 2. Leaks in irradiation facility containment units.
 3. Explosion of underground waste storage tanks.
- Nuclear reactors
 - 438 commercial nuclear generating units worldwide.
 - 104 of these units operate at 65 locations in the United States.
 - Accidents occur when barriers that isolate the heated radioactive water are breached and this water or materials from the radioactive core are released.
 - Large amounts of gamma and neutron energy are released without a nuclear explosion (criticality accident).
 - Cause large doses of whole body radiation exposure.
- Nuclear weapons
 - Detonation results in the tremendous release of thermal energy, gamma radiation, and α and β particles. Detected in vicinity of detonation and in fallout.
 - “Dirty bomb” is combination of radioactive materials and traditional explosives.

Radioactive Isotopes

- Numerous radioisotopes in use in many different industries.
- Radioisotope: Isotope that releases ionizing radiation during its decay.

Types of Radiation Exposure

- Ionizing radiation causes direct and indirect damage to tissue.
- Directly, radiation impacts the target molecule and causes damage. In DNA, mutations may arise, resulting in neoplasm or cell death.
- Indirectly, radiation impacts a molecule and creates a reactive species (free radicals) that may chemically react with organic molecules in cells, altering their structure or function.
- Usually, time and oxygen allow the organism to repair radiation damage; molecular scavengers such as glutathione help protect against free radicals. When these systems are overwhelmed by large doses of radiation, permanent damage may occur.
- May occur alone or simultaneously
 - Perceived radiation injury (fear out of proportion to actual danger, anxiety symptoms)
 - External contamination
 - Internal contamination
 - Partial-body irradiation
 - Whole body irradiation

Preparing for Arrival of Victims

- Emergency department preparation
 - Separate entrance is established.
 - Area for decontamination/treatment is established.
 - Pregnant women, nonessential equipment, personnel are removed.
 - Equipment and radiation supply kits are brought from storage (dosimeters, collection containers, survey meters).
 - Boundaries are set to delineate clean from contaminated areas. Radiation signs and floors are covered with nonskid plastic.
 - Ventilation system is turned off to prevent contamination of rest of hospital if airborne contamination is a possibility.
- Obtain detailed account of incident
 1. What radioactive substances were involved?
 2. What type of exposure occurred?
 3. How many victims?
- Arrival of patients
 - Emergency team don protective clothing and dosimeters.
 - Contaminated clothing/items are placed in bags and containers.
 - No one should leave radioactivity triage area/treatment area unless cleared by a radiation safety officer.
 - Emergency intervention/treatments should not be delayed because of contamination.
 - Mass casualty scenarios may involve giving only palliative care for those who received a known lethal dose of radiation.

Diagnosis

- History: Location of incident, duration of exposure, interval between exposure and evaluation, activity and location at time of exposure, occupation.
- Physical: ABCs of CPR, vital signs, neurological assessment, GI exam, hematologic exam (skin as well).
- Initial laboratory: Complete blood count (CBC) with differential, platelet count, and initial chemistries. Time of CBC must be carefully noted. Serial CBCs for 6 to 12 hours for at least three samples.

External Contamination

- Radioactive materials are deposited on patient's skin or clothing.
 - Dose from external contamination to patient or medical staff is rarely significant.
 - Main hazard is the spreading of contamination in the environment or potential for internalization.
 - Radionuclide itself not important immediately; important to know whether or not it emits beta, gamma, or alpha radiation.
 - An externally contaminated child should have all clothing removed, preferably at the scene.
 - Once medically stable, analysis with Geiger or alpha counters to determine sequence for decontamination of intact skin.
 - To assess internal contamination, saline-water swabs should be taken of all orifices and wounds and assessed for radioactivity.
 - Decontamination
 - Debridement of open wounds; remove as much debris as possible. Metallic fragments should be removed with thongs or forceps.
 - Copious irrigation of wounds with saline until free of radioactivity; then cover wounds with waterproof dressings.
 - Contaminated burns should be treated as thermal burns.
 - Mouth: Frequent tooth brushing and gargling if oral cavity contaminated. Gastric lavage indicated if radioactive substance swallowed.
 - Eyes: Rinse from Inner canthus to outer canthus; avoid contamination of nasolacrimal duct.
 - Ears: Rinse auditory canal with saline if TM intact.
- Sponge with lukewarm soap and water.
- AVOID cold water, as it closes pores and traps radioactive materials.
- AVOID hot water, because it causes vasodilation and increases risk of absorption.
- AVOID further damage to skin, as this may increase risk of absorption.
- Sponged areas should be reevaluated every 5 minutes until activity is consistent with background levels.
- Hair should be clipped if washing is insufficient for decontamination; do not shave.

Internal Contamination

- Radioactive material enters body through
 1. Inhalation
 2. Ingestion
 3. Absorption through MM or skin
- Internally deposited radioactive material will continue to irradiate tissues until it decays to a stable isotope or is biologically eliminated.
- Biochemical nature of radionuclide determines if it is disseminated throughout the body or concentrated in a specific organ.
- Critical organ: Organ that receives the highest dose of radiation or is the most damaged by radiation.
- Identification of radionuclides is important for determining method of treatment.
- Internally deposited radionuclides are identified by radioanalysis of substances excreted from body (saliva, blood, feces, urine). Known as bioassay measurement.
- Collect urine and feces for 4 days to monitor excretion rate.
- If ingested, begin gut decontamination (emetics, gastric lavage).

External Irradiation

- General concepts:
 1. Acute dose gives more biologic damage than the same radiation dose over a more protracted period of time.
 2. Biologic injury at time of exposure, clinical signs, and symptoms manifest over time.
 3. Time of exposure to onset of symptoms is inversely related to radiation dose received.
 4. Penetrating types of radiation result in a whole body dose.
 5. Nonpenetrating types (alpha, beta) do not deliver a whole body dose.

Whole Body Radiation/Acute Radiation Syndrome (ARS)

- Characteristic signs and symptoms develop when an organism is exposed to significant doses of radiation over a short period of time.
- Known as acute radiation syndrome.
- Whole body dose of gamma radiation in excess of 2 Gy (200 rad) is the main cause of ARS.
- Four distinct phases:
 1. Prodromal phase
 2. Latent phase
 3. Manifested illness phase
 4. Recovery phase or death
- Prodromal phase:

First 48 hours following exposure, but may develop up to 6 days after exposure.

Early symptoms include anorexia, apathy, nausea, vomiting, diarrhea, fever, tachycardia, or headache.

Generally mild or absent at total body doses of 1 Gy or less.

Patients whose symptoms begin more than 2 hours after exposure were probably exposed to doses <2 Gy, recover in about 1 month.

Onset of symptoms within the first 2 hours usually indicates significant and potentially lethal exposures exceeding 2 Gy.

At high doses (e.g., 10 to > 20 Gy), prodromal symptoms occur in virtually all patients within minutes of exposure. Death in days to weeks.
- Latent phase:

Symptom-free interval that follows resolution of the prodromal phase.

May last 1 to 3 weeks with a dose <4 Gy (400 rads).

May last only a few hours with a dose above 15 Gy.
- Manifested illness phase:

Often divided into three dose-dependent subsyndromes:

 1. Hematopoietic syndrome (HS)
 2. GI syndrome
 3. Cardiovascular and CNS syndrome
- Overlap between the three subsyndromes.
- Hematopoietic syndrome:

First system to express injury from whole body irradiation. Symptoms seen from doses above 1.5 Gy.

Radiation damages lymphocytes and damages stem cells in the bone marrow and lymphatic system.

Rapid decline in lymphocytes is a hallmark of hematopoietic syndrome.

Granulocytes and platelets display an initial rise and then a decrease to a nadir at about 30 days.

Mild anemia: Effects are pancytopenia and immunosuppression with hemorrhage and infection principle causes of morbidity and mortality. Worse at 2–3 weeks.
- GI syndrome:

Doses higher than HS syndrome, 6–7 Gy.

Onset of N/V, diarrhea within hours of exposure.

Latent phase of 1 week and then reoccurrence of symptoms and pain.

Damage to GI mucosa leads to massive fluid loss and electrolyte disturbances.

Enteric flora often invades bloodstream leading to sepsis; immunocompromised state of HS does not help.

Few documented cases were all fatal.
- CNS/CV syndrome:

Doses above 20 to 30 Gy.

Immediate prostration; N/V; explosive, bloody diarrhea; hypotension.

Alterations in consciousness, lethargy, seizures, within hours of exposure.

Hypotension refractory to treatment.

Universally fatal with death in 24 to 72 hours, mainly from circulatory collapse.
- Pulmonary: Radiation doses above 8–9 Gy can damage the pulmonary system leading to pneumonitis, interstitial edema, and fibrosis.
- Lethal dose: LD 50/60:
 1. 4.5 Gy, assumes intensive medical care provided.
 2. 3.4 Gy, only first aid.

3. High survival rate in Chernobyl victims of doses ~6 Gy.

4. Cytokine administration and stem cell transplant; may raise LD 50/60% to 11 Gy.

Treatment of ARS

- Obtain labs, collect specimens, decontaminate.
- Alleviation of symptoms, pain management.
- Ultimate treatment goal is to provide support during periods of deficient defenses against infection and hemorrhage, until marrow recovers.
- Support includes IV fluids, transfusions (note: blood products should be irradiated), ABX, TPN, antifungal medications (*Candida* species most common in neutropenic patients).
- Monitor for HSV, CMV, and *Pneumocystis carinii* pneumonia.
- Family and patient should undergo HLA typing if bone marrow transplants possible. Doses above 8–9 Gy (11 of 13 Chernobyl patients who received transplants died; causes were multifactorial).
- Research into hematopoietic growth factors and cytokines (stimulate stem cells and reconstitute bone marrow).

Local Radiation Exposure

- Partial body exposures.
- Clinical picture consists of cutaneous changes.
- Doses above 2–3 Gy may present with erythema, itching. Occurs within hours.
- Faster occurrence signifies higher doses.
- Other changes include epilation, desquamation, and necrosis.
- Appear similar to thermal burns, but unlike thermal burns erythema may reappear, delayed onset of pain, and more chronic, severe pain. Exception: High dose radiation may give 3rd degree transdermal burn, pain immediate and excruciating. Surgical resection and grafting may be required.
- Treatment: Analgesics, routine burn care, surgical referral. PT and splinting may prevent contractures and preserve ROM.

Special Populations

- Prenatal: Fetal cells largely undifferentiated and highly proliferative. Damage depends on phase of gestation.
 - 0–2 weeks: Irradiation results in death with reabsorption or no obvious damage.
 - >2 weeks: Risk of congenital malformations due to organogenesis. After 7 weeks, organogenesis is complete with exception of CNS.
 - Most common injuries to CNS are MR and microcephaly.
 - Minimum exposure of 0.1 to 0.2 Gy needed for injury.
 - Fetal thyroid takes up iodine at 12 weeks.
- Children
- Goals of management:
 1. Limit exposure.
 2. Reduce further damage to child's cellular systems.Key is to distance child from site of exposure and decontaminate. Fallout affects children more due to smaller size and higher absorption. KI should be available in schools, nurseries, and so on if within 10 miles from a nuclear reactor.
- Elderly: More susceptible due to decreased bone marrow reserve and increased likelihood of co-morbidities.

Radiation Exposures during Pregnancy

Exposure of Pregnant Patients

- Prenatal doses from most properly performed diagnostic procedures present no increased risk of prenatal death, malformation, or mental impairment
- Higher doses such as those from therapeutic procedures can result in significant fetal harm

Exposures from Nuclear Medicine Studies

- Radionuclides such as iodine-131 cross the placenta and can pose fetal risks.
- After 10 weeks gestational age, the fetal thyroid accumulates iodine.
- High fetal thyroid doses from radioiodine can result in permanent hypothyroidism.
- If pregnancy is discovered within 12 hours of radioiodine administration, prompt oral administration of stable potassium iodine (60–130 mg) to the mother can reduce the fetal exposure.

Fetal Radiation Risks and Health Effects

- Radiation-related risks during pregnancy are related to the stage of pregnancy and absorbed dose.
- Risks are most significant during organogenesis and in the early fetal period, somewhat less in the 2nd trimester, and least in the 3rd trimester.

Gestational Age and Radiation Dose

- <2 weeks gestation (the time after conception): Exposure of >0.1 Gy (10 rads) is the death of the embryo.
- <13 weeks gestation: Permanent retardation of physical growth with increasing dose, particu-

larly above 1 Gy (100 rads). (Atomic bomb survivor data suggest about a 3–4% reduction of height at age 18 when the dose is greater than 1 Gy.)

- >26 weeks: The fetus is less sensitive to the non-cancer health effects of radiation exposure.
- Any time: Doses above 1 Gy (100 rads) increase the risk for miscarriage, neonatal death, and stillbirth.
- In all stages of gestation, radiation-induced noncancer health effects are not detectable for fetal doses below about 0.05 Gy (5 rads).

Malformations and CNS Effects from Fetal Exposure

- Malformations have a threshold of >~100–200 mGy and are typically associated with CNS problems.
- Fetal doses >1000 mGy can result in reduction in IQ, severe mental retardation, and microcephaly, particularly during 8–15 weeks and to a lesser extent at 16–25 weeks.
- Preconception irradiation of either parent's gonads has not been shown to result in increased risk of cancer or malformations in children.

Steps to Prevent Exposures

- Be aware of placement of radiological equipment in the workplace.
- Use personal protective shields and equipment.
- Review Material Safety Data Sheets to become familiar with reproductive hazards.
- Participate in all safety and health education, training, and monitoring programs offered by the employer.

Table 23.1 Radiation Exposures: Ionizings. Non-ionizing

Ionizing Radiation	Non-ionizing Radiation
<i>Emission</i>	<i>Ultraviolet rad</i>
Alpha: ↓ penetration unless inhaled (radon)	sun → UVA & B
Beta: ↑ Penetration, 32P	skin (B): sunburn, aging, ca
Gamma: ↑ penetration 131I	Eye: (A & B): photokeratitis (A), cataracts (B)
X-rays: synthetic gamma rays	<i>Visible light</i>
<i>Units of Measurement</i>	Laser → retinal burns
Energy (meV)	Blue-light welding → retinal burns
Exposure (R)	Flash blindness
Absorption (RAD)	<i>Infrared rad</i>
Equivalent (REM)	↑ Heat → burns + cataracts
<i>Sources of Exposure</i>	<i>Microwave/Radiofrequency</i>
Natural	↓ spermatogenesis
Medical	thermal cataracts
Miscellaneous	<i>Electromagnetic fields</i>
	Risks?
	No carcinogenesis

Table 23.2 Sources of Ionizing

Natural	Medical	Miscellaneous
Greatest source of exposure in man radon (80%), gamma rays (55%)	Manmade #2 source of exposure (20%)	Also manmade-little exposure
<i>Sources</i>		
#1 Cosmic ↑ air travel	#1 X-rays: CXR	#1 Atmospheric Nuclear Testing & Accidents: ⁹⁰ Sr, ¹³⁷ Cs, ¹³¹ I, ¹⁴ C
#2 Terrestrial: location-dependent- Rocky Mountains	#2 Radionuclides: diagnostic + therapeutic	#2 Nuclear Power
#3 Radionuclides in food/water/air: ⁴⁰ K, ¹⁴ C		

Table 23.3 Health Effects of Ionizing Radiation

Acute Effects	Delayed Effects
REMs → Tissue Damage	1. Carcinogenesis
0-100 Chromosomes	Leukemias (AML, CML)
100-200 N + V, Leukopenia	X-rays
200-600 N + V, BM	gamma rays
800-3000 Depression	Solid Tumors
SLough GI tract, death 1-2 weeks	Ewing's sarcomas (226Ra)
>3000 CV + CNS collapse, death 24-48 hrs.	Thyroid carcinoma
	Lung carcinoma (238)U
	Liver carcinoma (Thorotrast)
	2. Teratogenesis
	3. Cataractogenesis
	α, β, gamma ≥ 500 RADs

Pregnancy Confirmation and Evaluation

- In female patients of child-bearing age, an attempt should be made to determine parity prior to radiologic imaging.
- Notices should be posted in patient and work areas warning of radiation exposure hazards (e.g., “If it is possible that you might be pregnant, notify the physician or other staff before your x-ray examination, treatment, or before being injected with a radioactive material.”).

Radiation Exposure of Pregnant Workers

- Informed consent: The pregnant patient or worker has a right to know the magnitude and type of potential radiation effects that might result from *in utero* exposure.
- Communication should be related to the level of risk. Communication that risk is negligible is adequate for very low dose procedures (<1 mGy to the fetus).

- Pregnant employees may work in a radiation environment if assurance exists that the fetal dose can be kept below 1 mGy during the pregnancy.
- Research involving radiation exposure of pregnant patients should be discouraged.

Termination of Pregnancy

- High fetal doses (100–1000 mGy) during late pregnancy are not likely to result in malformations or birth defects, because all the organs have been formed.
- Termination at fetal doses <100 mGy is not justified based on current risk assessments.
- Fetal doses >500 mGy can cause significant damage, at which point termination may be considered.

Table 23.4 Radiation – Relevant Legislation

Act	Year	Agency	Regulates
Atomic Energy Act-Nuclear Regulatory Commission (NRC)	1950s	NRC	Nonmilitary uses of radioactive sources
Low Level Waste Policy Act	1980	NRC	Disposal of radioactive wastes Class A (low) → C (high) concentration radioactive wastes
Nuclear Waste Policy Act (NRC+ Dept. of Energy – DoE)	1982	NRC DoE	Spent nuclear fuel rods Spent nuclear fuel storage sites

Resources for Radiation Emergencies

Review NIOSH Publications

- National Occupational Research Agenda. DHHS (NIOSH) Publication No. 96.115: Discusses fertility and pregnancy abnormalities as 1 of 21 priority research areas.
- The Effects of Workplace Hazards on Male Reproductive Health. DHHS (NIOSH) Publication No. 96.132: Provides general information about reproductive hazards for men in the workplace and suggests methods for preventing exposures.

Additional Resources

- Department of Energy Radiological Assistance Program:
 - Oak Ridge Operations Office
 - P.O. Box E
 - Oak Ridge, TN 37380
 - (423) 576-1005, 24 hrs: (423) 481-1000
- www.ornl.gov/reacts
- <http://www.nrc.gov/reading-rm/contact-pdr.html>

Chemical and Biological Weapons and Warfare (CBW)

Chapter Outline

Definitions

- Chemical
- Biological

Chemical warfare and biological warfare similarities

Chemical warfare and biological warfare differences

History of chemical warfare and biological warfare

- Ancient and early history
- Modern history

Chemical weapons

- Principles of decontamination
- Nerve agents
- Blister agents
- “Blood” agents (cyanides)
- Pulmonary agents (poison “gas”)
- Riot control agents (tear “gas”)
- Incapacitating agents

Biological weapons

- Likely warfare scenarios
- Suspicious syndromes
- Biological warfare agents

Emergency responsiveness

- Biological attack
- Chemical attack

Hierarchies of prevention

- Biological attack
- Chemical attack

Definitions

Chemical

Chemical Warfare (CW)

- The intentional use of noxious or toxic chemicals as weapons designed to terrorize, incapacitate, injure, or kill mass groups of people.

Examples: Chlorine and Phosgene

- Both gases are frequently transported by rail for use in drinking water purification, and chemical and plastic manufacturing, and are ubiquitously available as potential, simple chemical weapons. Phosgene gas caused 85% of all gas deaths in World War I.

Biological

Biological Warfare (BW)

- The intentional use of either microorganisms or toxins produced by a variety of living organisms including viruses (smallpox), bacteria (*C. botulinum*), fungi (mycotoxins), and plants (ricin) to cause dysfunction or death in people, livestock, and/or agricultural crops.

Example: *Bacillus anthracis*

- The sporulating anthrax bacillus is the most environmentally stable, easily disseminated of all the Class A biological warfare agents.

Chemical Warfare and Biological Warfare Similarities

- CW and BW are both employed as weapons of terror or mass destruction.
- CW and BW often use the same delivery systems, including artillery shells, missiles, and bombs.
- CW and BW are both dispersed most effectively as aerosols or vapors.
- The atmospheric movement of CW and BW is determined primarily by wind and other weather conditions, especially temperature.
- Wearing appropriate personal protective equipment will prevent injury from both CW and BW.

Chemical Warfare and Biological Warfare Differences

<u>Differences</u>	<u>Chemical Weapons (CW)</u>	<u>Biological Weapons (BW)</u>
<u>Confirmation</u>	Easier: 2° rapid onset effects, odors, simple detectors.	Harder: 2° delayed onset effects; no color, no odors, taste; limited detectors.
<u>Incubation</u>	Immediate: minutes-hours.	Delayed: days-weeks.
<u>Distribution</u>	Close, downwind, nonrandom.	Widely dispersed & random.
<u>Persistence</u>	Liquids persist (VX & mustard); gases dissipate.	Non-persistent, biodegradable, except anthrax & communicable plague pn.
<u>1st Response</u>	HAZMAT/EMTs, fire, police.	EDs, GPs, public health officials.
<u>Decontamination</u>	Necessary & critical.	Unnecessary, except acute exposures.
<u>Treatment</u>	Antidotes, support.	Antibiotics, vaccines, support.
<u>Isolation</u>	Unnecessary.	Necessary only for smallpox & plague.

History of Chemical Warfare and Biological Warfare

Ancient and Early History

- 600 BC: Athenians poisoned enemy water sources with *green hellebore* (cardiotoxic veratrum alkaloids). Assyrians used ergot to contaminate grain crops and bread.
- 429 BC: Spartans vs. Athenians — Spartans burned tar-pitch and brimstone to intentionally release sulfur gas, which mixed with atmospheric water vapor and human mucosal and lung water, to create highly irritant, water-soluble sulfuric acid on mucosal and upper respiratory tract exposure.
- 67 BC: Mithradates V of Pontus forced Pompey's pursuing Roman legions into a Turkish valley where the local honey was poisoned with grayanotoxins from *Rhododendron* nectar.
- 1344–1346: The Tartars besieged the Genoans in the Black Sea port of Kaffa and catapulted plague corpses into the walled city, creating an intentional plague epidemic that fleeing Genoans spread to western Europe as the *Black Death*.

Modern History

Modern History of Chemical Warfare

- 1915: Germans — Ypres, Belgium, chlorine (Cl) gas.
- 1917: Germans vs. Allies, Ypres, mustard gas.
- 1918: Capt. L. W. Lewis, USA-synthesized Lewisite gas.
- 1936: Germany (G), tabun “gas” (GA); liquid organophosphates.
- 1938: Germany, sarin “gas” (GB); liquid organophosphates.
- 1944: Germany, soman “gas” (GD); liquid organophosphates.
- 1952: United Kingdom, VX vesicant liquid arsenic.

- 1963–1967: Egypt vs. Yemen — mustard and nerve (organophosphates) agents may have been used.
- 1980s: Iraq vs. Iran — tabun, soman. Kurds — sarin and possibly cyanide gas, 1000s killed by poison gas, primarily sarin.
- 1994: Matsumoto, sarin gas released by *Aum Shinrikyo* cult, 7 deaths.
- 1995: Tokyo, sarin gas released in subway system by *Aum Shinrikyo* cult, 12 deaths.

Modern History of Biological Warfare

- 1763: French and Indian War (U.S.) — British General Sir Jeffrey Amherst distributed smallpox-contaminated blankets to Native Americans allied with the French.
- World War I: Germans intentionally infected Allied livestock with *Bacillus anthracis* and glanders (*Burkholderia mallei*, formerly *Pseudomonas mallei*).
- 1936–1944: Manchuria, General Shiro Ishii, MD, Unit # 731, infected Chinese POWs and civilians with anthrax and plague.
- 1940: Porton Down, U.K. (British BW research), sheep infected with anthrax on Gruinard Island, off Scotland.
- 1941: Ft. Detrick, MD (U.S. BW research begins).
- 1978: Georgi Markov, Bulgarian double agent assassinated in London by KGB with a ricin pellet injected by an umbrella gun.
- 1979: Sverdlovsk, Russia, 66 anthrax deaths followed accidental release of weaponized anthrax from Russian BW facility.
- 1979–1983: USSR vs. Afghanistan — “yellow rain,” tricothecene mycotoxins may have been used on Afghan resistance. No delivery devices discovered.
- 1984: Oregon — Rajneeshee cult intentionally contaminated restaurant salad bars with *Shigella* spp.

- Sept.–Oct. 2001: Anthrax-spore-filled letters mailed along the east coast, causing 22 anthrax cases — 10 inhalational anthrax (4 deaths, 40% CFR) and 12 cutaneous anthrax (no deaths).
- CFR = 80% for occupational inhalation anthrax (wool sorter's disease).

Chemical Weapons

Principles of Decontamination

Objectives of Decontamination

- To prevent further absorption and spread of toxic substances on victims.
- To prevent contamination of others.
- To focus on CW and BW liquids, which can spread to others, and are more amenable to decontamination than gases.
- To focus on mass CBW exposure solutions; for example, all CW and BW victims must disrobe and then shower immediately prior to further decontamination procedures. This initial decontamination step could be simply and efficiently conducted at home.

Chemical Warfare and Biological Warfare Decontamination

- CW decontamination: (1) All nerve agents are hydrolyzed and inactivated by 1:10 dilutions or 0.5% solutions of household bleach; (2) sulfur mustard must be inactivated within 1–2 min; (3) copious water or soap and water showering also work well; (4) water irrigation alone works best for tear gas as caustic bleach exacerbates skin lesions.
- BW decontamination: (1) Initial disrobing, then soap and water showering; (2) 0.5% bleach, then water rinse also effective for BW.

Nerve Agents

Mechanisms, Properties, Toxicities

- Mechanism: Organophosphate (OP) acetylcholinesterase (AChE) inhibitors, related to reversible OP insecticides, that can complex with AChE irreversibly (in a reaction known as *aging*).
- German (G) agents: Tabun (GA), sarin (GB), soman (GD)—all are clear, volatile liquids, eas-

ily aerosolized (no GC agent, because GC = gonorrhea).

- Vesicant (V) agent: VX (UK), oily liquid, low volatility, persists in the environment.
- Toxicities: Soman > VX > sarin > tabun.
- Aging rapidity: Soman > tabun > sarin > VX (48 hours). 2-PAM is effective only for soman and VX and only in the therapeutic window before irreversible aging commences.

Cholinergic Toxidrome

- Hierarchy of symptom onset: Muscarinic > nicotinic > CNS
- Muscarinic (DUMBBELS): Diarrhea, urination, miosis, bronchospasm, bronchorrhea, emesis, lacrimation, salivation. Miosis > headache > dyspnea > nausea and vomiting > eye pain > diplopia. Miscellaneous: localized sweating.
- Nicotinic: Weakness > fasciculations > sphincter incontinence > flaccid paralysis.
- Central nervous system (CNS): Apnea, respiratory depression, loss of consciousness, seizures.

Pretreatment AChE Protection

- Pyridostigmine: A reversible carbamate AChE inhibitor that can block nerve agent access to the AChE enzyme by occupying binding sites, thus protecting a portion of AChE from potential complexing with nerve agent and later aging irreversibly. Pyridostigmine binding can be later reversed with pralidoxime (2-PAM). To offer protection, primarily from tabun and soman (not sarin and VX), 20–40% of AChE must be inhibited by pyridostigmine pretreatment. Pretreatment also enhances the efficacy of both atropine and 2-PAM reversal therapy.

Post-Exposure Management

- Anti-muscarinic treatment: Atropine in 2-mg doses titrated to endpoints of reversing bradycardia and wheezing, and drying up secretions.

Mark I kits contain one 2-mg *AtroPen* injector. Only atropine drops can reverse miosis and eye pain.

- Anti-nicotinic treatment: Pralidoxime (2-PAM) reactivates the OP-AchE complex prior to aging. Mark I kit also contains a 600-mg 2-PAM *ComboPen* that must be co-administered with atropine.
- Anti-epileptogenic treatment: Anticonvulsants, principally diazepam 10 mg — the other part of the *ComboPen* in Mark I kits.

Blister Agents

Sulfur Mustard

- Properties: Yellow-brown oily liquid, mustard-horseradish odor, decreased volatility, increased environmental persistence, high temperatures, high vaporization, permeates clothes and skin.
- Mechanism: Alkylating agent (like nitrogen mustard) that alkylates sulfhydryl bonds blistering skin and lungs; breaks DNA crosslinks; inhibits glycolysis; depletes ATP and glutathione.
- Clinical: Skin > lungs > eyes; necrotic bullae, especially in warm moist skin areas (axilla, perineum, groin, neck); 1st to 3rd degree burns. Lungs: cough, bronchospasm, tracheobronchitis, pseudomembranes formation. Eyes: miosis, lacrimation, photophobia, blepharospasm, corneal burns, rarely blindness. Miscellaneous: early nausea and vomiting, later bone marrow depression.

Post-Exposure Management

- Decontaminate with water and 5% bleach solution.
- Unroof all large blisters and bullae (do not contain mustard).
- Apply atropine eye drops to eyes and petroleum jelly to lids to prevent adhesive synechiae formation.
- Inhaled O₂, bronchodilators, and mucolytics.
- Bronchoscopic removal of obstructive tracheobronchial (“diphtheritic”) pseudomembranes.
- Early, elective tracheal intubation.

Lewisite

- Properties: 2-Chlorodivinyldichloroarsine, oily, colorless liquid; more volatile, but less environmentally persistent than mustard, also more amenable than mustard to water and bleach inactivation.
- Mechanism: Same as arsenic and mustard, alkylates sulfhydryl groups causing skin and lung blistering, inhibits glycolysis, depletes glutathione.
- Clinical: Similar to mustard but immediately painful; blistering not as severe as mustard.

Post-Exposure Management

- Water or 5% bleach decontamination.
- Administer specific antidote: British anti-Lewisite (BAL) IM, still used to chelate arsenic and other heavy metals, such as lead and mercury.
- Other heavy metal chelators can also be used: DMSA, DMPS.

“Blood” Agents (Cyanides)

Agents, Properties, Mechanisms

- Agents: Used ineffectively in World War I by France initially (hydrogen cyanide, cyanogen chloride), then Austria (cyanogen bromide). 1980s: used by Iraq against Iran and Kurds of Northern Iraq.
- Properties: Active ingredient, hydrocyanic acid, is lighter than air, dissipates rapidly, and either kills victims or permits quick recovery, except for cyanogen chloride, which can cause delayed pulmonary edema.
- Mechanism: Initially felt to exert systemic toxicity via bloodstream; actually inhibits cellular respiration in mitochondria.

Decontamination and Treatment

- Decontamination: Initial disrobing, then soap and water showering.
- Treatment: O₂, cyanide kit = amyl nitrite, sodium thiosulfate, support.

- Miscellaneous treatment: Cyanocobalamin (B_{12}); methylene blue; correct metabolic acidosis; support urine output.
- Treatment mechanism: (1) Oxidize ferrous oxyhemoglobin (oxyHb^{+2}) to ferric methemoglobin (metHb^{+3}) with nitrates to bind free CN^- and form cyanomethemoglobin, (2) competitively pull CN^- out of the ferrous oxyhemoglobin moiety with thiosulfate to form urine-excretable thiocyanate, (3) reverse methemoglobinemia with methylene blue.
- Properties: Volatile oily liquids disseminated as aerosols, sprays, and incendiary bombs for crowd control with rapid onset, short duration of action, and high safety profile. Severe reactions and deaths (CN, CS) from status asthmaticus possible after closed space exposures.

Clinical Manifestations and Treatment

- Clinical: Rapid onset of eye and skin burning, lacrimation, conjunctival injection, photophobia, blepharospasm, sneezing, rhinorrhea, cough, chest tightness, bronchorrhea, bronchospasm, possibly status asthmaticus.
- Treatment: Initial disrobing then immediate copious cold water irrigation. 5% bleach solutions are contraindicated and could exacerbate injuries. Lidocaine gel patches for topical treatment of capsaicin exposure.

Pulmonary Agents (poison “gas”)

Agents, Properties, and Mechanisms

- Agents: Phosgene ($>$ chlorine) caused 85% of gas deaths in World War I; both gases are used extensively in industry, along with NO_2 .
- Properties: More water-soluble chlorine forms a yellow-green cloud with pungent odor; more insoluble phosgene hydrolyzes in mist, forming a white cloud with pleasant odor of freshly mown grass or hay.
- Mechanism: All pulmonary agents hydrolyze in lung water, forming HCl, which burns tracheo-bronchial mucosa causing rapid pulmonary edema.

Clinical Manifestations and Treatment

- Clinical: Rapid onset of cough, dyspnea, chest pain, rhinorrhea, lacrimation, frothy and bloody pulmonary edema within 2–6 hours, delayed respiratory failure common; phosgene said to cause smoked tobacco to taste bad.
- Treatment: Mostly supportive with O_2 and aerosolized inhalation of sodium bicarbonate to neutralize HCl. Early, elective tracheal intubation highly recommended.

Riot Control Agents (tear “gas”)

Agents and Properties

- Agents: All are intense dermal and mucous membrane irritants and lacrimators and include (1) CN: chloracetophenone = Mace®; (2) CS: chlorobenzilidene malonitrile; and (3) OC: oleoresin capsicum = capsaicin = pepper spray.

Incapacitating Agents

Vomiting Agent

- DM: Diphenylaminearsine (Adamsite).
- Mechanism: Arsinine hydrolyzes sulfhydryl groups in mucosa, inhibits glycolysis, depletes glutathione, like Lewisite.
- Clinical: Arsinine gas induces initial eye and upper airway irritation, followed by headache, malaise, nausea, and severe vomiting with dehydration.
- Treatment: Supportive with IV fluids.

Sedating Agent

- BZ: Quinuclidinyl benzylate.
- Mechanism: A CNS-acting anticholinergic 25× more potent than atropine. (Note: Israel, 1991: $>$ 200 casualties occurred from self-inflicted atropine poisoning during the first Gulf War).
- Clinical: Anticholinergic syndrome = “Mad as a hatter, blind as a bat, hot as Hades, dry as a bone.” Initial dry mouth and mydriasis, then delayed onset of incapacitating drowsiness, incoordination, reduced cognition, delirium, increased awakening over 2–3 days.
- Treatment: Supportive only.

Biological Weapons

Likely Biological Warfare Scenarios

- Most probable: The intentional aerosolized release of: (1) anthrax spores (*Bacillus anthracis*) > (2) crystalline botulinum toxin (*Clostridium botulinum*) > (3) plague (*Yersinia pestis*) > smallpox (*Variola minor*) > (4) tularemia (*Pasteurella tularensis*).
- Less likely: Intentional contamination of drinking water, because microorganisms and toxins will be inactivated by dilution, aeration, and chlorination.
- Least likely: Intentional contamination of food supplies, because of limited impact and slow progression; will only occur as isolated BW terrorism events.

Suspicious Syndromes

- Acute respiratory distress and fever and no history of trauma or chronic disease = anthrax, plague, tularemia, ricin, Staphylococcal enterotoxin B.
- Eruptive fever and rash = smallpox.
- Flu-like illness and sepsis = tularemia, arenavirus hemorrhagic fevers, brucellosis, Q fever.
- Acute bilateral descending flaccid paralysis = botulism.
- Blistering syndromes = nitrogen mustard, VX, tricothecene mycotoxins (T2), Staphylococcal enterotoxin B.

Biological Warfare Agents

Anthrax

- Microbiology: *Bacillus anthracis* is a large, spore-forming Gram-positive bacillus (rod) that grows in lengthening chains and produces three antigens: protective antigen that is attenuated for the anthrax vaccine and facilitates endocytosis of other two antigens, edema factor (causes massive swelling), and lethal factor (releases TNF and IL-1).

- Pathology: Inhaled spores enter thoracic lymphatics and germinate within mediastinal lymph nodes, causing hemorrhagic mediastinitis with pleural effusions, but no pneumonia. Cutaneous form is due to direct skin inoculation and is characterized by black eschar and massive edema (unlikely in BW release).
- Differential diagnosis: Pulmonary embolism, dissecting thoracic or thoracoabdominal aneurysm.
- Diagnosis: Positive chest x-ray with widened mediastinum and pleural effusions, positive Gram stain and positive culture and sensitivity testing on sputum and blood, ELISA, PCR.
- Treatment: Ciprofloxacin 400 mg IV every 8 hours, or doxycycline 200 IV every 8 hours, or penicillin 2 MU every 2 hours and streptomycin IM or gentamicin IV.
- Prevention: Ciprofloxacin 500 mg or doxycycline mg 100 orally bid for 4–6 weeks and 6-shot vaccine, or every 8 weeks without the anthrax vaccine.

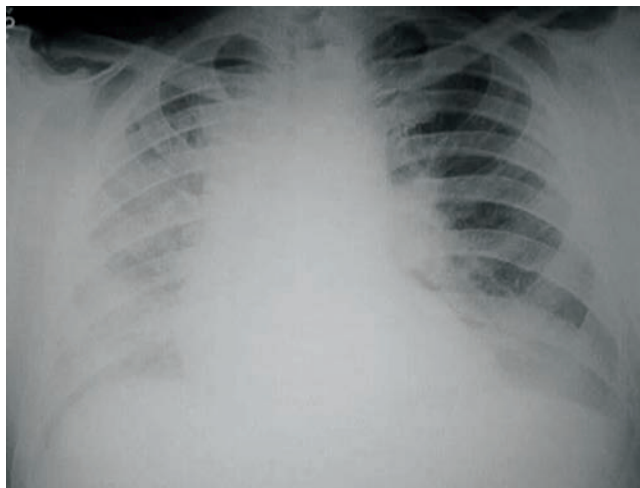


FIGURE 24.1 Pulmonary Anthrax. Frontal chest radiograph of a patient with pulmonary or inhalation anthrax that demonstrates the characteristic widening of the mediastinum, bilateral pleural effusions, bilateral perihilar infiltrates, and clear peripheral lung fields. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

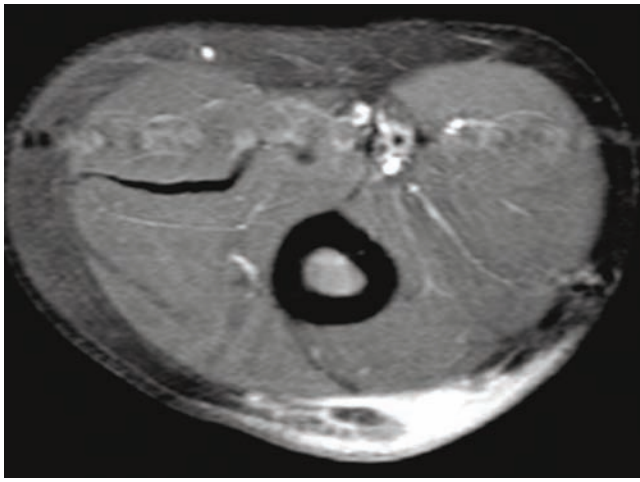


FIGURE 24.2 Cutaneous Anthrax 1. Axial magnetic resonance image (MRI) with intravenous gadolinium contrast enhancement of the arm of a patient with cutaneous anthrax that demonstrates massive lymphedema and enhancement of the subcutaneous fat in the lateral compartment. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

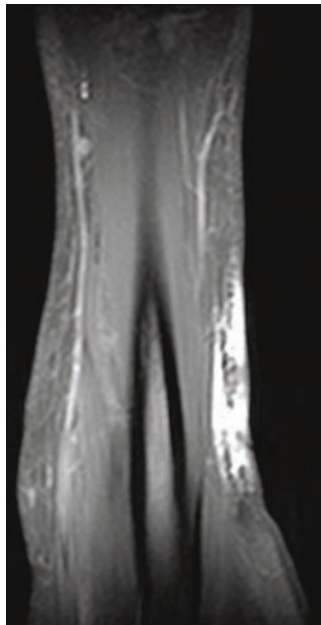


FIGURE 24.3 Cutaneous Anthrax 2. Coronal magnetic resonance image (MRI) with intravenous gadolinium contrast enhancement of the arm of a patient with cutaneous anthrax that demonstrates massive lymphedema and enhancement of the subcutaneous fat in the lateral compartment. (Courtesy of Carlos R. Gimenez, M.D., Professor of Radiology, LSU School of Medicine, New Orleans, LA.)

Plague

- **Microbiology:** *Yersinia pestis* is a Gram-negative, safety-pin shaped coccobacillus.
- **Pathology:** Bubonic plague occurs in endemic areas from plague-infected rat flea bites and is characterized by fever, malaise, regional buboes, and possibly sepsis. Pneumonic plague occurs with a 2–3 day incubation period after direct respiratory contact or BW release and is characterized by headache, fever, chills, cough, hemoptysis, severe pneumonia, then respiratory failure with cardiovascular collapse and terminal coagulopathy.
- **Differential diagnosis:** Community acquired pneumonia, hantavirus pulmonary syndrome, meningococemia.
- **Diagnosis:** Chest x-ray with severe pneumonia; sputum, blood, or bubo aspirate for Gram-negative coccobacilli with bipolar, safety-pin shape Gram-negative staining characteristics; blood culture with growth in 24 hours, often misdiagnosed as *Y. enterocolitica*; antibodies detected by IgM ELISA, antigens detected by PCR.
- **Treatment:** Streptomycin IM 30 mg/kg/day for 10 days, and doxycycline 200 mg IV push, then 100 mg IV every 12 hours for 10 days; or gentamicin IV 5 mg/kg for 10 days.
- **Prevention:** Tetracycline 500 mg orally four times daily for 7 days, or doxycycline 100 mg orally twice daily for 7 days.

Tularemia

- **Microbiology:** *Franciscella tularensis* is an aerobic and environmentally stable, non-spore forming, Gram-negative coccobacillus with an epizootic reservoir in rabbits and ixodid tick transmitting vectors.
- **Pathology:** A very low inoculum (<50 organisms) may be transmitted via direct contact with infected rabbits, tick bites, or aerosolized organisms (secondary to BW or just mowing grass). Contact results in ulceroglandular > oculoglandular > oropharyngeal (ingestion) tularemia with ulcers at entry sites and regional lymphadenopathy. Inhalation results in pneumonic tularemia with abrupt onset of high fever, productive cough, pleuropneumonitis, hemoptysis, bilateral hilar adenopathy, sepsis

(typhoidal tularemia), and terminal respiratory failure.

- Differential diagnosis: Influenza, mycoplasma pneumonia, adenoviral or atypical community-acquired pneumonias.
- Diagnosis: Positive chest x-ray with bilateral pneumonia and hilar adenopathy; mediastinum not widened; positive gram stains or fluorescent antibody stains and positive culture on ulcers, sputum, blood; serological antigen detection by ELISA and PCR.
- Treatment: Streptomycin 30 mg/kg/day bid for 14 days, or gentamicin 3–5 mg/kg/day IV for 14 days.
- Prevention: No vaccine, doxycycline 100 mg orally every 12 hours for 14 days, or tetracycline 2 g/day orally for 14 days.

Ricin

- Microbiology: Ricin is a lethal toxin produced by the castor bean plant that inhibits protein synthesis at the ribosomal-messenger RNA level.
- Pathology: On parenteral exposure, ricin causes a septicemic syndrome with fever, leukocytosis, shock, and death within 24–72 hours. Double-agent Georgi Markov was assassinated by the KGB via ricin pellet injection (London, 1978). On inhalation exposure, ricin causes a pulmonary syndrome with fever, weakness, cough, hypoxia, pulmonary edema, and terminal respiratory failure.
- Differential diagnosis: Staphylococcal enterotoxin B, community-acquired atypical pneumonias.
- Diagnosis: Chest x-ray initially normal, then the ricin-poisoned patient rapidly develops pneumonia and pulmonary edema; serological antigen detection by ELISA on nasal swabs, sputum, or blood.
- Treatment: Respiratory support in ICU.
- Prevention: An investigational new drug (IND) toxoid vaccine under development by the U.S. Army.

Staph Enterotoxin B (SEB)

- Microbiology: SEB-1 is a super-antigenic bacterial toxin that produces profound activation of the immune system when either inhaled or ingested.

- Pathology: If inhaled, SEB-1 causes a pulmonary syndrome with a 3- to 12-hour incubation period that is characterized by prolonged fever, chills, headaches, myalgias, persistent coughing (for weeks), chest pain, hypoxia, and an incapacitating pneumonia that is rarely fatal. If ingested in spoiled dairy products, SEB-1 causes food poisoning characterized by severe vomiting and dehydration.
- Differential diagnosis: Ricin, tularemia.
- Diagnosis: Positive chest x-ray with pneumonia, antigen and antibody detection by ELISA.
- Treatment: Supportive.
- Prevention: No toxoid vaccine, respirator mask.

Smallpox

- Microbiology: *Variola minor* is a highly contagious DNA pox virus, related to chicken pox and monkey pox.
- Pathology: After a typical 14-day incubation, smallpox causes high fever, malaise, prostration, headache, backache, myalgias, cramping abdominal pain, delirium, and a characteristic centrifugal rash with the synchronous appearance and resolution of initial red macules, then vesicles, pustules, ulcers, crusts, and pitted scars, most prominent on the face and extremities. CFR = 30%.
- Differential diagnosis: Chickenpox—has a characteristic centripetal rash with asynchronously developing and resolving red macules, vesicles, pustules, ulcers, crusts, scabs, and shallow scars, most marked on the neck and trunk.
- Diagnosis: Viral culture, antigen detection by ELISA and PCR.
- Treatment: None, possibly ribavirin or cidofovir.
- Prevention: Calf-lymph vaccinia vaccine intradermally every 10 years.

Brucellosis

- Microbiology: *Brucella* is a small gram-negative coccobacillus with a zoonotic reservoir in domestic livestock: cattle (*B. abortus*), pigs (*B. suis*), and goats (*B. melitensis*).
- Pathology: A very low inoculum of *Brucella* may be inhaled (<1 week incubation) or ingested (7–60 day incubation) and causes a

nonspecific illness characterized by prolonged undulant fevers, chills, malaise, weakness, joint pain, early acute bloody diarrhea, later chronic fatigue and depression; complications include osteomyelitis and SBE. Often misdiagnosed as fibromyalgia/chronic fatigue syndrome.

- Differential diagnosis: Streptococcal SBE, chronic fatigue syndrome, fibromyalgia.
- Diagnosis: Blood culture, antigen and antibody detection by ELISA.
- Treatment: Doxycycline 200 mg/day orally and rifampin 600–900 mg/day orally for 6 weeks.
- Prevention: Avoid undercooked meats and unpasteurized milks and cheeses.

Botulism

- Microbiology: *Clostridium botulinum* is an aerobic, spore-forming, Gram-positive bacillus that produces 8 toxins (A–H), which can be aerosolized.
- Pathology: After a short 1- to 5-day incubation period, botulism is characterized by afebrile, acute descending flaccid paralysis and CN palsies, causing ptosis, diplopia, mydriasis, dysarthria, dysphonia, dysphagia, weakness, hypotonia, paralysis, and terminal respiratory failure. CFR = 50%.
- Differential diagnosis: Guillain-Barré syndrome — a subacute post-infectious ascending weakness, paralysis, and sensory loss.
- Diagnosis: Antigen detection by ELISA in gastric aspirate, vomitus, stool, or blood. Spares cranial nerves, toxin acts peripherally only.
- Treatment: Supportive and trivalent equine antitoxin for toxins A–E, or heptavalent equine Fab antitoxin for serotypes A–E.
- Prevention: IND pentavalent toxoid vaccine for serotypes A–E under development by the U.S. Army.

Miscellaneous Biological Warfare: Q-Fever

- Microbiology: Q-fever is caused by *Coxiella burnetii*, a Gram-negative Rickettsia with an epizootic reservoir in wild mammals and domestic livestock (cattle, sheep, goats) and a tick vector; transmitted to man via fecal or gestational aerosols and not tick bites; extremely stable environmentally, with a very low infective inoculum (1 organism).

- Pathology: Nonspecific illness after 10–28 days incubation with malaise, high fever, rigors, myalgias, no rash, painful hepatosplenomegaly, persistent pneumonitis; complicated by myocarditis, endocarditis, and encephalitis. Prolonged convalescence, low CFR (<1%) without endocarditis.
- Differential diagnosis: Influenza, infectious mononucleosis, brucellosis, leptospirosis, toxoplasmosis.
- Diagnosis: Positive chest x-ray with patchy pneumonic infiltrates, serologic antigen detection by complement fixation, no Weil-Felix (*Proteus* agglutination) reaction.
- Treatment: Tetracycline 500 mg orally every 6 hours for 1 week, or doxycycline 100 mg orally every 12 hours for 1 week.
- Prevention: Post-exposure tetracycline or doxycycline every 1 week within 8–12 days; IND vaccine under development; avoid domestic livestock aerosols, especially of fecal and gestational products.

Miscellaneous Biological Warfare: Nipah Virus

- Microbiology: Nipah virus is a previously unrecognized paramyxoviral zoonosis of Malaysian fruit bats, closely related to the Hendra virus of Australia. Caused an outbreak of febrile encephalitis in Malaysian pig farmers in 1998–1999 with 260 cases and 110 deaths.
- Pathology: Natural reservoir in flying fruit bats that transmit mild infections to pigs characterized by mild encephalitis and pneumonitis. Close contact and aerosol transmission to man characterized by febrile encephalitis, areflexia, segmental myoclonus, hypertension, and tachycardia; CFR = 50%.
- Differential diagnosis: Equine encephalidides, LaCrosse encephalitis.
- Diagnosis: Positive MRI demonstrates high-signal-intensity lesions throughout brain, viral identification in cerebrospinal fluid by electron microscopy, viral isolation from CSF.
- Treatment: Ribavirin
- Prevention: Cull infected swine.

Miscellaneous Biological Warfare: Tricothecene Mycotoxins

- Microbiology: Easily aerosolized mycotoxins that are produced by several filamentous molds, including *Stachybotrys* > *Fusarium* > *Myrothecium* and *Trichoderma*, and, like ricin, inhibit protein synthesis.
- Pathology: Mycotoxins can cause immediate toxicity on exposure to intact skin and mucosa by inducing inflammatory lesions with early necrosis of skin and mucosa, and throughout tracheobronchial tree. Onset of action is more rapid than with liquid CWs, like mustard and VX. If ingested, mycotoxins can cause alimentary toxic aleukia with fever, chills, gastroenteritis, bone marrow suppression, and sepsis.
- Differential diagnosis: Vesicant CW exposure, especially sulfur mustard, and acute radiation sickness (*dirty bomb*).
- Treatment: Supportive only.

Emergency Responsiveness

Biological Attack

- Report possible attack to local Office of Public Health, Centers for Disease Control, Police Department, Federal Bureau of Investigation.
- Diagnose and characterize etiologic agent(s).
- Treat all victims specifically and supportively.
- Provide prompt, specific prophylaxis to all “worried well,” possibly exposed.

Chemical Attack

- Report possible attack to local Office of Public Health, Centers for Disease Control, Police Department, Federal Bureau of Investigation.
- Decontaminate all exposed immediately in appropriate response site with hot zone, surrounding decontamination or warm zone, and outer supporting or cold zone — all aligned upwind.
- Diagnose and characterize etiologic agent(s).
- Triage and treat all victims specifically and supportively, following decontamination.

Hierarchies of Prevention

Biological Attack

- Primary prevention by vaccination (smallpox, anthrax, plague)
- Antibiotic treatment and prophylaxis
- Surveillance and warning systems
- Irradiation of mail/food
- Use electronic over regular, snail mail
- Lab precautions and infection control
- Public health education and communication
- Personal protective equipment (PPE)—HEPA masks, Level A—total self-contained breathing apparatus (SCBA)

Chemical Attack

- Plant/property security at safety-sensitive sites
- Surveillance and warning systems
- Chemical release characterization network
- Track controlled chemicals
- Public health education and communication
- Engineering controls—health ventilation and air conditioning intakes, decontamination systems
- PPE—gas masks, SCB A: Level A—total SCBA, Level B—SCBA or respirator, Level C—air purifier

Workplace Substance Abuse Monitoring

Chapter Outline

Introduction

Americans with Disabilities Act (ADA)

Federal regulations

Components of a comprehensive drug-free workplace program
Definition of a disabled individual
ADA and employment drug testing

Epidemiology

Some measures of the impact of drugs in the workplace
Marijuana is the most commonly used illicit drug in the United States
Types of drug testing

Chemical dependency

Substance Dependency (APA, DSM-IV)
Tolerance develops
Withdrawal develops
Recurrent substance abuse
Experimental substance abuse
Recreational substance abuse
Circumstantial substance abuse

Abused substances

Five basic categories of psychoactive substances
Opioids/opiates
Sedatives
Psychedelics/hallucinogens
Four basic categories of psychoactive of stimulant substances

Substance abuse professionals (SAPs)

Substance abuse professionals medical review of officer (MRO)

Medical review officers (MROs)

The practical MRO
Medical review officer qualifications

Employee assistance programs (EAPs)

Rehabilitation

Rehabilitation and individual treatment
Rehabilitation and Therapeutic Medications
Rehabilitation and Psychiatric Medications
1991 Omnibus Transportation Employee Testing Act (PL102-143)
Omnibus Transportation Employee Testing Act 1991

Alcohol testing

Random alcohol testing

Drug testing

DOT drug testing procedures

Chain of custody (CoC)

Unique screening characteristics of commonly abused drugs
Opiate metabolism

MRO responses

Medical Miranda

Introduction

Americans with Disabilities Act (ADA)

- “The Federal Government, as the largest employer in the nation, can and should show the way towards achieving drug-free workplaces through a program designed to offer drug users a helping hand...” Executive order 12564, 1986.
- The ADA prohibits discrimination against individuals with disabilities in employment, public services and transportation, public accommodations, and telecommunications services. The ADA also impacts drug-free workplace efforts. Legislated 1992–1994; enacted 1994.

Federal Regulations

Components of a Comprehensive Drug-Free Workplace

- 1986: EXECUTIVE ORDER 12564 initiated drug testing of over 1.8 million safety- or security-sensitive federal employees in executive branch agencies.
- 1988: U.S. Department of Health and Human Services (DHHS) MANDATORY GUIDELINES FOR FEDERAL WORKPLACE DRUG TESTING PROGRAMS set scientific and technical standards for drug testing of federal employees and for certification of drug testing laboratories.
- 1988: U.S. Department of Transportation (DOT) REGULATIONS impact 4 million private-sector employees in DOT-regulated industries, requiring sanctions, training/education, and testing.
- 1988: DRUG-FREE WORKPLACE ACT required federal contractors and grantees to provide a drug-free workplace written drug policy, employee drug abuse awareness, and sanctions for convictions of drug crimes in the workplace. (No drug testing required.)
- 1989: U.S. Nuclear Regulatory Commission (NRC) RULES required nuclear power facilities to implement fitness-for-duty testing programs.
- 1991: OMNIBUS TRANSPORTATION EMPLOYEE TESTING ACT (PL 102-135) enacted by Congress and mandated drug and alcohol testing for over 6 million transportation industry employees.
- 1994: DOT ALCOHOL MISUSE RULES mandated breath alcohol testing of transportation employees.

- 1994: Americans with Disabilities Act (ADA).
- Formal written policy
- Employee assistance program (EAP)
- Supervisor training
- Employee education
- Methods for deterring and detecting illicit drug users (i.e., drug testing)

Definition of a Disabled Individual

- An individual with a disability “has a physical or mental impairment that substantially limits one or more major activities of daily living (e.g., caring for oneself, walking, seeing, hearing, speaking, and working), a record of such impairment, or who is regarded as having such an impairment.”

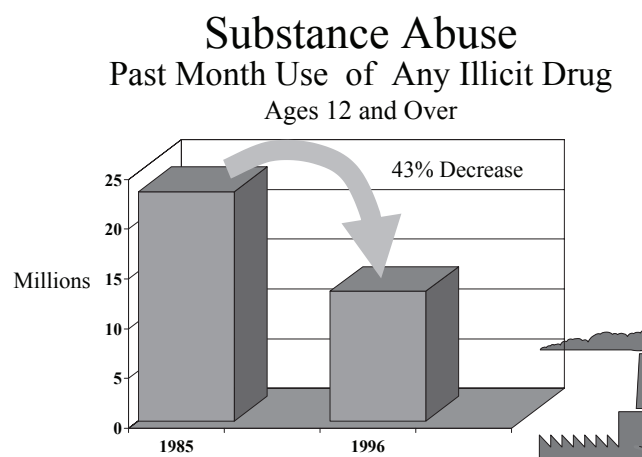


Table 25.1 Clinical Laboratory Improvement Act + Amendments (CLIA)

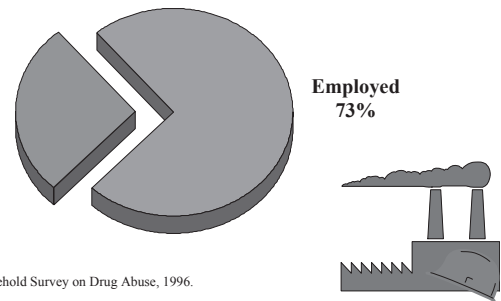
	Forensic Testing	Workplace Drug Testing	Testing as Part of a Treatment Program
Drugs	Not covered	Not covered	Covered
Alcohol	Not covered	Not covered	Covered except by breathalyzer

ADA and Employment Drug Testing

- The ADA does not interfere with an employer taking appropriate action for alcohol or drug abuse on the job.
- The ADA does not impact an employer's ability to perform drug testing for job applicants or employees.
- Drug tests are not medical examinations under ADA and are not subject to the same restrictions as other employment physicals.

Substance Abuse

The Majority of Current Drug Users Are Employed
(Current Users of Illicit Drugs, Ages 18 and Over)



Source: National Household Survey on Drug Abuse, 1996.

Epidemiology

Some Measures of the Impact of Drugs in the Workplace

- Absenteeism
- Accidents and injuries
- Increased health care utilization
- Lost productivity
- Theft, property damage, reduced security
- Increased training requirements

Marijuana Is the Most Commonly Used Illicit Drug in the United States

- The 1996 National Household Survey estimated the number of marijuana users as:
 - Occasionally – 8.6 million
 - Monthly – 9.8 million
 - Weekly – 6.1 million

Types of Drug Testing

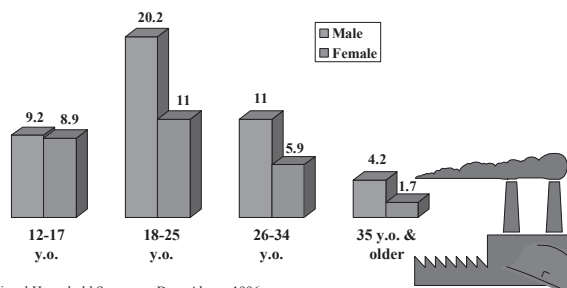
- Applicant testing
- Accident/unsafe practice testing
- Reasonable suspicion testing
- Follow-up to treatment testing
- Random testing
- Voluntary testing

Goals of changing opiate testing cut-offs:

- To substantially reduce the total number of specimens reported as positive for opiates by laboratories, but verified as negative by the Medical Review Officer (MRO).
- To shift the emphasis of testing for opiates to the deterrence and detection of heroin use.
- To reduce unnecessary and excessive costs of re-testing without compromising the original drug deterrent objectives.

Substance Abuse

Percent Past Month Use of Any Illicit Drug by Age and Sex



Source: National Household Survey on Drug Abuse, 1996.

Substance Abuse

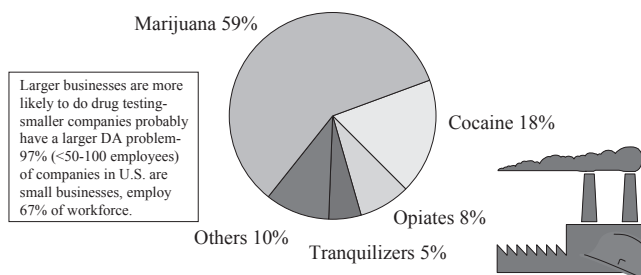
Current Illicit Drug Use Among 18-49 Year Olds Full-Time Employed by Industry



Source: Drug Use Among U.S. Workers, 1993.

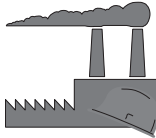
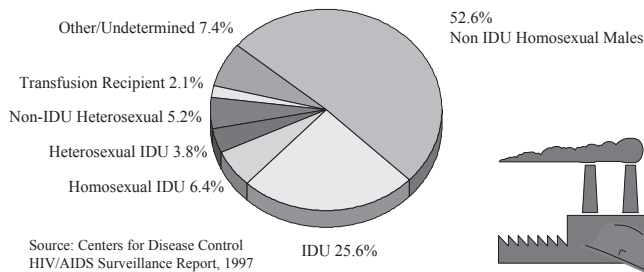
Substance Abuse

Drug Distribution of Positive Urine Tests Among U.S. Workforce Tested by SKB Clinical Labs 1/97 - 6/97



Substance Abuse

U.S. Adult/Adolescent AIDS Cases
by Exposure Category
(Cumulative through June 1997, N=604,178)



5 ng/mL or more delta-9-THC acid; several exceeded 15 ng/mL.

- Hemp oil is more of a problem than hemp seed ingestion.

Drug Tests

- The Americans with Disabilities Act does not impact an employer's ability to perform drug testing for applicants or employers.
- Drug tests are not medical examination under ADA and are not subject to the same restrictions as other employment physicals.

Urine Drug Tests after Ingesting Food Products Containing Hemp Seeds

- Specimens that showed immunoreactivity (not necessarily = or > cutoff) were tested by gas chromatography/mass spectrometry; some screened positive, most did not.
- Gas chromatography/mass spectrometry results were 0 or very close to 0 ng/mL; none were close to cutoff (50 ng/mL).
- Immunoreactivity was likely due to cannabinoids other than delta-9-THC acid; may be a problem for on-site testing.

Urine Drug Tests after Ingesting Hemp Oil

- 14 employees screened positive at 20 ng/mL; 7 screened positive at 50 ng/mL; 2 screened positive at 100 ng/mL.
- All specimens were tested by gas chromatography/mass spectrometry; 14 of the 18 contained

Omnibus Transportation Employee Testing Act of 1991

- Requires drug and alcohol testing of safety-sensitive employees in the aviation, rail, truck, bus, and mass transit sectors.
- Types of testing include:
 - Pre-employment
 - Reasonable suspicion
 - Random
 - Post-accident
- All drug testing is to be conducted according to the HHS Mandatory Guidelines.

Table 25.2 HHS Cut-offs

Drug/Metabolite	Initial (ng/mL)	Confirmation (ng/mL)
Marijuana metabolite	50	15 (delta-9-THC acid)
Cocaine metabolite	300	150 (benzoylecgonine)
Opiates	2000	2000 (morphine), 2000 (codeine)
Phencyclidine	25	500 (phencyclidine)
Amphetamines	1000	500 (amphetamine), 500 (methamphetamine ^a)

^a To be reported there must be 200 ng/mL amphetamine.

Table 25.3 Revisions to Opiate Cut-offs, Effective in 1998

Drug/Metabolite	Initial (ng/mL)	Confirmation (ng/mL)
Opiates	2000	
Morphine		2000 ^a
Codeine		2000
6-Acetylmorphine		10

^a If morphine equals or exceeds 2000 ng/mL, then the laboratory must analyze for 6-acetylmorphine by gas chromatography/mass spectrometry (6-MAM).

Chemical Dependency

- A positive toxicology screen alone does not equate with chemical dependency, substance dependence, or substance abuse.

Substance Dependency (APA, DSM-IV)

- “A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period.”
 - Tolerance
 - Withdrawal
 - The substance is often taken in larger amounts or over a longer period than was intended.
 - There is a persistent desire or unsuccessful effort to cut down or control substance use.
 - A great deal of time is spent in activities necessary to obtain the substance or recover from its effects.
 - Important social, occupational, or recreational activities are given up or reduced because of substance use.
 - The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

Tolerance Develops

- A need for markedly increased amounts of the substance to achieve intoxication or desired effect, OR
- Markedly diminished effect with continued use of the same amount of the substance.

Withdrawal Develops

- The characteristic withdrawal syndrome for the substance, OR
- The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.

Recurrent Substance Abuse

- Recurrent substance use results in a failure to fulfill major role obligations at work, school, or home.
- Recurrent substance use in situations in which it is physically hazardous.
- Recurrent substance-related legal problems.
- Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance.

Experimental Substance Abuse

- Short-term, random trials of one or more drugs, motivated by curiosity or a desire to experience an altered mood state.

Recreational Substance Abuse

- Substance abuse that occurs in a social setting among friends or acquaintances who desire to share an experience that they define as both acceptable and pleasurable. Use is both voluntary and patterned.

Circumstantial Substance Abuse

- Substance abuse for the purpose of achieving an anticipated effect in order to cope with a specific problem, situation or condition of a personal or vocational nature.

The U.S. Substance Abuse and Mental Health Services Administration (SAMHSA) Five Drugs of Abuse

- Amphetamines/methamphetamines
- Cocaine
- Marijuana
- Opioids
- Phencyclidine (PCP)

Abused Substances

Five Basic Categories of Psychoactive Substances

1. Opioids/Opiates
2. Sedatives
3. Psychedelics/Hallucinogens
4. Stimulants
5. Inhalants

Opioids/Opiates

- Heroin
- Morphine
- Codeine
- Propoxyphene
- Hydromorphone
- Diphenoxylate
- Hydrocodone
- Dihydrocodone
- Oxycodone
- Pentazocine
- Methadone
- Meperidine
- Fentanyl
- Sufentanil
- Butorphanol

Opioid Use and Induced Disorders

- Dependency
- Abuse
- Intoxication
- Withdrawal
- Intoxication delirium
- Induced psychotic disorder, with delusions
- Induced psychotic disorder, with hallucinations
- Induced mood disorder
- Induced sexual dysfunction
- Induced sleep disorder

Opioids/Opiates — Routes of Administration

- Heroin, morphine, Dilaudid®, fentanyl, sufentanil, and meperidine are usually injected.
- Codeine, oxycodone, hydrocodone, MS Contin®, pentazocine, and methadone are usually taken orally.
- Opium is usually smoked. Heroin and morphine may be smoked or insufflated nasally.
- Fentanyl may also be administered by patch.

Signs and Symptoms of Opioid Intoxication

Physical

- Nodding out
- Drowsiness
- Respiratory depression
- Constricted pupils
- Nausea
- Vasodilation (“flush & rush”)
- Slurred speech

Psychological

- Impaired judgment
- Impaired social functioning
- Euphoria
- Impaired attention
- Impaired memory

Signs of Opioid Overdose

- Slow and shallow breathing
- Clammy skin
- Convulsions
- Coma
- Death

Signs and Symptoms of Opioid Withdrawal (A “flu-like” syndrome)

- Dysphoric mood
- Nausea or vomiting
- Muscle aches
- Lacrimation
- Rhinorrhea
- Dilated pupils
- Diarrhea
- Yawning
- Fever
- Insomnia

Sedatives

Sedative Examples

- Alcohol — beer, wine, spirits
- Benzodiazepines — Valium®, Librium®, Ativan®, Xanax®, Halcion®, Restoril®, Klonopin®, benzodiazepine-like Ambien®
- Barbiturates — phenobarbital, secobarbital, pentobarbital, butabarbital, amobarbital
- Barbiturate-like — chloral hydrate, meprobamate, glutethimide, carisprodol (Soma®)

Sedative-, Hypnotic-, or Anxiolytic-Induced Disorders

- Dependence
- Abuse
- Intoxication
- Withdrawal
- Intoxication delirium
- Withdrawal delirium
- Induced persistent amnesic disorder
- Induced psychotic disorders
 - With delusions
 - With hallucinations
- Induced mood disorder
- Induced anxiety disorder
- Induced sexual disorder
- Induced sleep disorder

Alcohol

- Approximately 66% of all adult Americans take at least one alcoholic drink in the course of a year.

- Men drink more than women.
- Women metabolize alcohol slower than men.
- Among males 18 to 29 years of age, 77% report drinking alcohol.
- Approximately 47% of alcoholics meet the criteria for another psychiatric disorder.
- Alcohol withdrawal should be treated.

Common Alcohol Withdrawal Signs and Symptoms

- Nausea and vomiting
- Tremor
- Paroxysmal sweats
- Anxiety
- Agitation
- Tactile disturbances
- Auditory disturbances
- Seizures
- Visual disturbances
- Headache, head fullness
- Disorientation and clouding of sensorium
- Increased blood pressure and pulse rate
- Hypertension

Benzodiazepines

- Widely prescribed for:
 - Anxiety disorders
 - Muscle relaxation
 - Seizure disorders
 - Sleep disturbances
 - Alcohol withdrawal
- Anxiolytic properties are reinforcing
- May affect motor performance
- No U.S. National Institute of Drug Abuse (NIDA) laboratory standards

Barbiturates

- About 4% of the population have taken barbiturates for nonmedical purposes.
- Males ages 26 to 34, living in large metropolitan areas, are more likely to have used barbiturates.
- Barbiturates abuse is less popular now, preempted by abuse of the safer benzodiazepines.
- Some increase in prescribing barbiturates is now noted in states that monitor benzodiazepine use.

Common Sedative Withdrawal Symptoms

- Anxiety
- Irritability
- Insomnia
- Fatigue
- Headache
- Muscle twitching or aching
- Tremor, shakiness
- Nausea, loss of appetite
- Observable depression
- Depersonalization
- Increased sensory perception
- Abnormal perception or sensation of movement
- Seizures
- Death

Psychedelics/Hallucinogens

- Hallucinogens consist of a variety of compounds that alter perceptions and feelings.
- Hallucinogens rarely produce hallucinations.
- Phencyclidine (PCP) is often grouped as a hallucinogen, but is really a dissociative anesthetic, related to ketamine:
 - Ketamine dissociates awareness from the body.
- Ketamine permits abusers to self-induce altered perceptions and feelings.

Hallucinogen Use and Induced Disorders (DSM-IV)

- Dependence
- Abuse
- Intoxication
- Persisting perceptual disorder (Flashbacks — LSD, PCP)
- Intoxication
- Delirium
- Induced psychotic disorders
 - With delusions
 - With hallucinations
- Induced mood disorder
- Induced anxiety disorder

Psychedelics/Hallucinogens Examples

- Marijuana (THC)
- Phencyclidine (PCP)

- LSD
- Psilocybin (mushrooms)
- Mescaline (peyote)
- Methylenedioxymethamphetamine (MDMA, Ecstasy)
- Methylenedioxyethamphetamine (MDE)

Marijuana

Marijuana Route of Administration

- Most often smoked:
 - Onset of effects within several minutes. Effects may last approximately 2 hours.
- May be taken orally:
 - Onset of effects in 30+ minutes.
 - Effects may last 3–5 hours.
- Variable absorption of THC in digestive system

Inhalants

- Glue
- Gasoline
- Solvents
- Correction fluids
- Anesthetics
- Paint/lacquer thinners
- Polishes
- Amyl nitrates

Inhalant Uses and Induced Disorders

- Dependence
- Abuse
- Intoxication
- Intoxication delirium
- Persisting dementia
- Induced psychotic disorder:
 - With delusions
 - With hallucinations
- Induced mood disorder
- Induced anxiety disorder
- Dementia/organic brain syndromes

Lysergic Acid Diethylamide LSD

- No legal therapeutic use
- Schedule I drug

- A little drug goes a long way (doses average only 50 to 100 micrograms)
- Detected in urine using radioimmunoassay (RIA) at levels of 0.5 ng/mL or above
- Not a National Institute of Drug Abuse (NIDA) five substance of abuse
- Doses often sold on the street on blotter paper
- May also be used in pill or liquid form
- Efficient oral and digestive system absorption
- The blotter paper or sticker on to which the LSD is deposited is often a pop-art form; “Beavis and Butt-Head,” for example
- There can be a “brand name” quality to the blotter paper
- Blotter → LSD “stickers”

Mescaline – Peyote

- Mescaline is found in peyote and San Pedro cacti of the desert in Southwest United States and Latin America
- Typical dose: 300–500 mg or 6–12 peyote “buttons”
- About 1/2000th the potency of LSD
- About 1/20th the potency of psilocybin
- Duration: 6+ hours
- Efficient oral and digestive system absorption

Psilocybin/Psilocin

- Found in numerous species of mushrooms
- About 1/100th the potency of LSD
- Typical dose: 10-20 mg
- Duration: 4–6 hours
- Efficient oral and digestive-system absorption
- Dry weight in mushrooms is about 1%
- Psilocin is a dephosphorylated moiety of psilocybin

Phencyclidine – PCP

- Routes of administration
 - smoked
 - oral ingestion
 - intranasal snorting
 - intravenous injection

Four Basic Categories of Psychoactive of Stimulant Substances

- Cocaine
- Amphetamine/Methamphetamine
- Nicotine
- Caffeine

Stimulants

Signs and Symptoms of Stimulant Overdose

- Agitation
- Increased body temperature (hyperthermia)
- Hallucinations
- Convulsions
- Arrhythmias
- Death

Signs and Symptoms of Stimulant Withdrawal

- Dysphoric mood
- Fatigue
- Vivid, unpleasant dreams
- Increased appetite
- Psychomotor retardation or agitation
- Insomnia or hypersomnia

Treatment Issues for Stimulant Users

- An overdose of stimulants constitutes a medical emergency that requires immediate attention. Seizures and cardiac arrhythmias may require medications. Anxiety reaction can be managed by reassurance. Sedative-hypnotic medications may be required.

Stimulant Use and Induced Disorders

- Dependence
- Abuse
- Intoxication
- Withdrawal
- Intoxication delirium
- Induced psychotic disorders
 - With delusions
 - With hallucinations
- Induced mood disorder
- Induced anxiety disorder
- Induced sexual disorder
- Induced Sleep Disorder

Routes of Administration

- May be injected, snorted, smoked or consumed orally.

Crack Cocaine

Illicit Dispensing Characteristics

- Small vials
- Basic substance
- Not water soluble
- Inexpensive
- Usually smoked

Cocaine Routes of Administration Profile

- Intranasal:
 - Onset in 30 seconds to 2 minutes
 - Peak levels of 150 ng/mL
 - Post-drug dysphoric state
- Intravenous:
 - Onset in 15 seconds or less
 - Peak levels in 3–5 minutes
 - Duration 15–20 minutes
- Smoking:
 - Onset in 10 seconds or less
 - Peak levels in 3–5 minutes
 - Duration of high 15 minutes

Amphetamines

Amphetamine/Methamphetamine Routes of Administration

- May be injected, snorted, smoked, or consumed orally.

Signs and Symptoms of Amphetamine Intoxication

- Tachycardia or bradycardia
- Pupillary dilation
- Hypertension or hypotension
- Perspiration or chills
- Nausea or vomiting
- Psychomotor agitation or retardation
- Evidence of weight loss
- Muscular weakness, respiratory depression, chest pain, or cardiac arrhythmias
- Confusion, seizures, dyskinesias, dystonia, or coma
- Impairment in attention or memory

Physical Signs of Injection Drug Use

- Track marks along veins
- Needle puncture sites

Track Marks along Veins

- Arms
- Forearms
- Dorsa of hands
- Dorsa of feet
- Thighs (inguinal crease)
- Neck
- Dorsal veins (penis or clitoris)

Dermatologic Masquerades, Hiding Track Marks

- Tattoos
- Arm hair
- Body hair
- Abscesses
- Old scars

Substance Abuse Professionals (SAPs)

- A trained health professional engaged in the counseling and monitoring of substance abuses.
- The SAP may determine the number and the frequency of the unannounced follow-up testing.
- Additional counselor whose certification is recognized by DOT (e.g., National Association of Alcoholism and Drug Abuse Certification Commission Certification)

Substance Abuse Professional vs. Medical Review Officer (MRO)

- With the advent of 1994 regulations, the SAP has broader functions than the MRO, a licensed physician. The SAP is involved in alcohol testing. The MRO is not. The SAP is involved in assistance determination. The MRO is not. The SAP is involved in follow-up testing. The MRO is not.

SAPs: Who Can Be One?

- A licensed physician (MD or DO)
- A licensed or certified:
 - Psychologist
 - Social worker
 - Employer Assisted Program (EAP) Officer or providers

SAPs: What Do They Do?

- The generic function of the SAP is to evaluate an employee who has tested positive for alcohol or drugs to determine what assistance, if any, the employee needs in resolving problems associated with alcohol misuse or controlled substance abuse.

SAPs – What Else Do They Do?

- Through a second evaluation, the SAP determines whether an employee who has tested positive for alcohol or drugs has properly followed the prescribed rehabilitation program, where offered or required.

Table 25.4 SAP vs. MRO

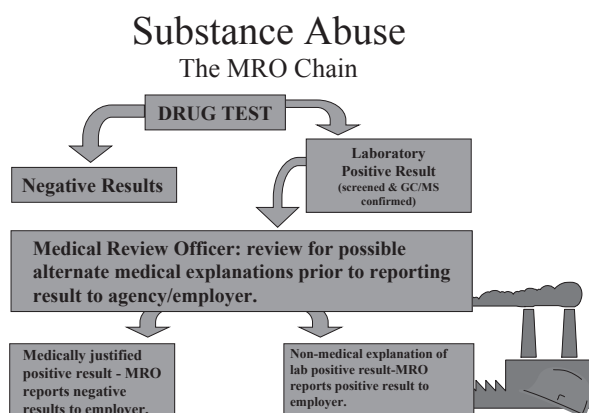
Activity	SAP	MR
Interpret drug test results		X
Evaluate employee for help for drug use	X	
Evaluate employee for help for alcohol use	X	
Determine employee compliance	X	
Determine need for cross-training	X	
Determine follow-up testing	X	

Medical Review Officers (MROs)

- Must be a licensed physician with knowledge of substance abuse disorders.
- Must afford an opportunity for the tested individual to discuss the test results prior to making a final decision to verify a test as positive.
- Must review all medical records made available by a tested individual when a confirmed positive could have resulted from a legally prescribed drug.
- To confirm heroin, urine must contain 6-monoacetylmorphine (6-MAM) or MRO must find clinical evidence, such as venous track marks, (in addition to the positive urine test) of drug abuse.
- Only the MRO can authorize reanalysis of the original sample.
- If the MRO finds a legitimate medical explanation, the specimen is reported as negative.

California Proposition 215 and Arizona Proposition 200

- The Medical Review Officers (MROs) shall not accept a prescription, or the verbal or written recommendation of a physician, for a Schedule I substance as a legitimate medical explanation for the presence of a Schedule I drug or metabolite in a Federal employee/applicant specimen.
- This policy applies to all Federal agencies. This affects approximately 1.8 million employees in all 50 states and territories, as well as those stationed abroad.



The Practical MRO

- The MRO–Employee Interview
 - Documentation
 - “Medical Miranda”
 - Interview tips
 - The denying donor
 - Common excuses
- 5- and 14-day rule
- Specimen not suitable
- Opiates
- Amphetamines
- Split samples
- Reporting issues
- Return to work determination
- Commercial driver’s license (CDL) exams and controlled substances testing
- Shy bladder evaluation
- Reporting requirements
- DOT guidance to Third Party Administrators (TPAs) and MROs
- Announcement to change opiate cutoffs
- MRO/LAB conflict of interest prohibitions

Medical Review Officer Qualifications

- “The Medical Review Officer shall be a licensed physician (MD or DO) responsible for receiving laboratory results generated by an employer’s drug testing program who has knowledge of substance abuse disorders and has appropriate medical training to interpret and evaluate an individual’s confirmed positive test result together with his or her biomedical history and any other relevant biomedical information.”
— 49 U.S. CFR Part 40.3

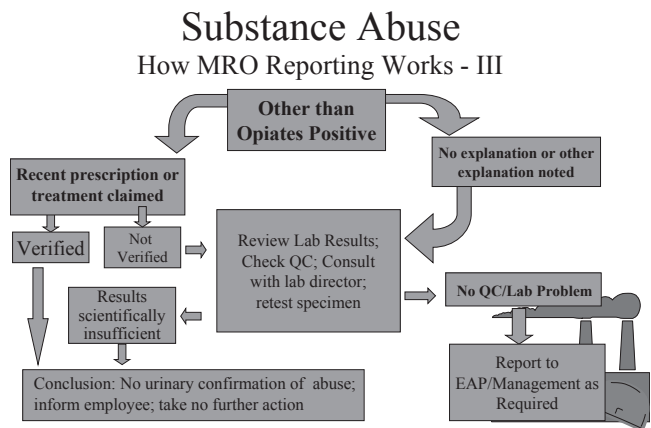
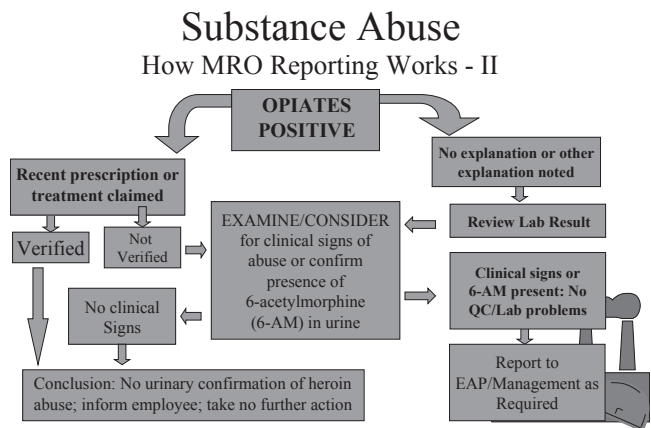
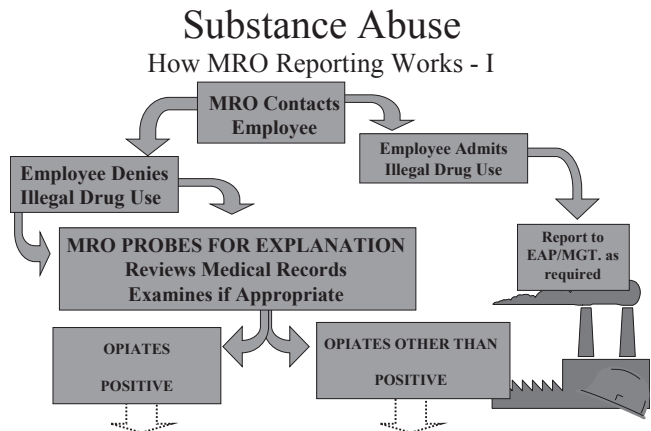
The Medical Review Interview Is Not...

- A normal encounter with a patient
- A popularity contest
- A way to build your practice
- A criminal investigation

- A personal crusade
- A tool for use by the employer
- A chemical dependency evaluation
- A normal doctor-patient relationship

The Medical Review Interview

- Use Standard Form
- One size fits all?
- Review of COC
 - fatal flaws
 - correctable flaws
 - noncritical flaws
- Identify self and affiliation
- Confirm identity of the donor (have donor confirm last 4 digits of SS#)
- Inquire about collection procedures
- Present medical Miranda
- Inquire re: illicit drug use
- Offer split sample or re-test (required by RSPA, USCG)



Employee Assistance

Employee Assistance Programs (EAPs)

- Programs concerned with drug, alcohol, and other problems that have an adverse impact on work performance in businesses and industries.

Employee Assistance Program Functions

- Educating employees about alcohol and drugs
- Exploring personal problems affecting work performance
- Training supervisors as referral agents
- Consulting on specific cases
- Referring employees to treatment
- Evaluating employees for return to work

EAP Prevalence

- Only one third of all private worksites in the United States with 50 or more full-time employees have an EAP.
- However, 55% of all U.S. employees in private worksites with 50 or more employees are covered by EAP services.

Employee Assistance Program Organizations

- Internal (operated by the company)
- External (operated by an outside contractor)
- Operated by management or union
- May do simple evaluations or more complex ones
- May offer short-term or long-term treatments

Table 25.5 Size of Worksites with EAPs

Worksite Size	% with EAPs
50–99 employees	20.8
100–259 employees	33.2
250–999 employees	48.4
1000+ employees	76.1

Table 25.6 Types of Industries with EAPs

Industry	% with EAPs
Manufacturing	33.3
Wholesale/retail	33.7
Communication/utilities/transportation	53.4
Finance/realty/insurance	41.5
Mining/construction	20.4
Services	25.4

Rehabilitation

- Rehabilitation begins with the detection of the proscribed substance and the admission by the positive employee that there is a problem.
- Rehabilitation is often linked with some form of treatment providers.
- U.S. Department of Transportation (DOT) regulations DO NOT mandate that an employer provide treatment for an affected employee.
- Naltrexone can be used as an opioid blocker for those at risk for using opioids.
- Antabuse® may be used as an aversive for those at risk for using alcohol.
- Methadone can be used for opioid maintenance for those unable to remain opioid-free. (Cannot be used under DOT regulations. Methadone is proscribed by DOT)

Rehabilitation and Individual Treatment

- Medical detoxification
- Outpatient psychoeducation
- Outpatient relapse prevention
- Residential therapeutic treatment
- Family therapy
- Self-help support systems:
 - 12-step programs (e.g., Alcoholics Anonymous, Narcotics Anonymous, Cocaine Anonymous, Methamphetamine Anonymous)
 - Rational Recovery or Secular Organizations for Sobriety (SOS)
- Toxicology screens

Rehabilitation and Therapeutic Medications

- Naltrexone (ReVia®) can be used as an anti-craving agent for alcoholics.

Rehabilitation and Psychiatric Medications

- Antidepressants may be beneficial for early withdrawal states or for concomitant primary depression.
- Antipsychotics may be necessary for those suffering from psychotic symptoms either secondary to or concomitant with substance abuse.

1991 Omnibus Transportation Employee Testing Act (PL 102-143)

- Enacted after NYC transit (subway) accident.
- Mandated drug and alcohol testing programs in transportation industries.
- Affected over 7 million safety sensitive employees.
- Required DOT to issue implementing regulations.

Table 25.7 Principles and Devices for Breath-Alcohol Analysis^a

Principle	Typical Commercial Device	Features ^a
Chemical oxidation and photometry	Breathalyzer models 900, 900A	4
Electrochemical oxidation/fuel cell	Alco-Sensor II, III	2, 5, 7
Gas chromatography	BAC DataMaster Intoxilyzer Models 1400, 5000	1, 2, 3, 5 1, 2, 3, 5
Infrared spectrometry	A.L.E.R.T. Model 14	2, 5, 7

^a Features:
 1 = Automatic purge and zero
 2 = Digital result readout
 3 = Integral printer
 4 = Liquid reagents
 5 = Reagentless
 6 = Compressed gas required
 7 = Battery operated

- Applies to aviation, railroad, transit, and commercial motor vehicle operations.
- Requires pre-employment, post-accident, reasonable suspicion, and random urine drug testing.
- Mandates use of DHHS procedures for urine drug testing.
- Requires “split specimens” for drug testing.

Omnibus Transportation Employee Testing Act 1991

- Includes all common driver’s license (CDL) required vehicle operators.
- Includes air traffic controllers.
- Requires opportunity for treatment for individuals who engage in prohibited conduct.

Prohibited Alcohol Conduct

- Performance of safety-sensitive functions is prohibited under the following conditions:
 - While having an indicated alcohol concentration of greater of 0.04 or greater.
 - While using alcohol.
 - Within four hours (flight crew: 8 hours) after using alcohol.
 - Use of alcohol for 8 hours following an accident or until tested, when an employee knows of the accident and an alcohol test is required.
 - Refusal to submit to a required alcohol test.

Alcohol Testing

- Post-accident
- Random
- Reasonable suspicion
- Return-to-duty and follow-up

Random Alcohol Testing

- Initial annual rate of 25%.
- Adjustable (10–50%) based on “violation” rate.
- Random alcohol testing must be conducted just before, during, or just after performance of safety-sensitive duties.
- Random testing must be announced and must be conducted immediately after notification of employee.

Alcohol Testing Procedures

- Alcohol testing must be conducted using testing devices listed on a National Highway and Traffic Safety Administration (NHTSA) conforming products list.
- Alcohol testing procedures include accuracy, reliability, and confidentiality protections.
- Screening test may be conducted using an alcohol screening device (ASD) or an evidential breath testing device (EBT).
- Confirmation evidential breath test must be completed within 30 minutes of presumptive positive screening test (≥ 0.02) and must use EBT.
- Blood alcohol test not authorized under DOT rules.

Drug Testing

DOT Drug Testing Procedures

- Require testing in federally certified laboratories.
 - Five classes of drugs.
 - Two separate analytical processes.
 - Stringent internal and external quality control procedures.
 - Employee confidentiality protected.
- Include physician review and interpretation of test results.
 - Established MRO concept and functions.
 - Provide for donor interview.
 - Protect employee confidentiality.

Receipt of Drug Test Results

- Lab reports all test results to MRO.
- Lab reporting of test results cannot be by telephone.
- Lab must send chain-of-custody (CoC) copy on all results.
- Collection site must send MRO copy of CoC directly to MRO.
- No routine reporting of quantitative levels (except opiates).
- Receipt of test results must be secure and confidential.

Review of Negative Test Results

- Administrative review only.
- CoC fatal flaws/corrective statements.
- Conducted by MRO staff.
- MRO signature stamp/staff initials OK.

Review of Positive Test Results

- MRO copy of CoC.
- Lab copy of CoC — signed by Certifying Scientist.

- Special requests (quantitative levels, additional analysis). DOT → opiate specification.

Review of Atypical Test Results

- Dilute specimens
- Unsuitable for testing specimens.
- Adulterated specimens

Atypical Specimen Analysis: Dilute Specimen

- Report as negative — must report.
- Inform employer of dilute result, including possible explanations for dilution.
- Employer decision on direct observation for subsequent collections.
- Do not require re-testing of donor.

Atypical Specimen Analysis: Specimen Unsuitable for Testing

- Explore tampering possibility.
 - Inform donor of adulteration suspicion.
 - Inform employer that specimen was unsuitable.
 - Report is cancelled.
 - Re-testing of donor under direct observation.

Interpretation of Positive Results

- Donor contact
 - If unable to contact donor, contact company representative.
 - Once notified by company representative, donor has five days to contact MRO for an explanation.
 - If donor fails to contact MRO, or expressly refuses to discuss test results with MRO, result is verified as positive.

- If MRO or company cannot contact donor, verify as positive after 14 days.

- Medical interview
 - Must be conducted by physician, MRO.
 - Limits of confidentiality explained.
 - Review of medications and medical procedures.
 - Offers an opportunity for split specimen analysis.
 - Offers opportunity for re-analysis of primary specimen (U.S. Resource Services and Pipelines Administration [RSPA] and U.S. Coast Guard [USCG] only).
 - Document donor contact, medical interview, and findings.

Split Specimen (MRO Processing)

- Inform donor of opportunity to have split urine specimen analyzed on verified positive test.
- Process request for split analysis (72 hour window for donor decision).
- Provide written request to laboratory.
 - Include specimen ID#, drug(s) to second lab.
- Review split analysis result from second lab.
- Report reconfirmation result to employer and donor.
- Report failure to reconfirm to employer, donor, and DOT.
- Failure to reconfirm, inability to locate split, or lack of split collection requires cancelled test result.

Interpretation of Opiate Results

- Obtain codeine and morphine quantitation.
- Order 6-mono-acetylmorphine (6-MAM) analysis, if appropriate >2000 µg/mL cut-off exceeds.
- Obtain medical history regarding opiate use.
- Demonstrate clinical evidence of unauthorized use of opiates needed.
- Establish policy on prescription drug sharing, foreign medication use, and use of “old” prescriptions.

Reporting Results

- Telephone reporting to employer authorized
- Ensure confidentiality of reporting
- Provide written documentation of verified result
- Verified positives must be signed by MRO
- Federal Aviation Administration (FAA) requires MRO reporting to FAA on pilots

Urine Specimen Collection Procedures

- Collection site personnel — need some training in collection techniques
- Preparation of collection site
- Supplies and equipment
- Chronological steps of collection process
- Process ensures specimen identity, security and integrity
- Based on principles of search and seizure of evidence — a legal procedure
- Custody and control form documentation required
- A search and seizure collecting evidence (urine) must assure integrity of evidence

Specimen Collection Supplies

- Specimen collection “kit”
 - Specimen bottle(s)*
 - Shipping container
 - Specimen bag/pouch
 - Collection container
 - Temperature device
- Custody and Control Form
 - 6 or 7 copies of form
 - Bottle seal(s)/label(s) attached
 - Shipping container seal attached
 - Requires donor’s and collector’s signatures
 - “Chain of custody” block
- Pen, rubber gloves, bluing agent, tape

* Must be a freshly voided specimen

Chain of Custody (CoC)

“Fatal Flaws” Resulting in Cancelled (or Rejected) Urine Specimen

- No preprinted specimen ID number
- No donor SSN or ID# unless noted in remarks
- No collector signature on collector statement*
- Incomplete CoC block* — indicated by absence of any of the following:
 - Collector name
 - Shipping entity
 - Date
 - Purpose of CoC entry
 - Recoverable by signed statement
- On Positive Results:
 - No donor signature on specimen*
 - No certifying scientist signature

* Recoverable by signed statement

Specimen Rejection Criteria

- Fatal CoC error
- Quantity-not-sufficient (QNS) specimen (30 mL minimum).
- Bottle seal broken or absent
- Specimen ID# on bottle and CoC form do not match
- Specimen obviously contains “foreign matter.”

Specimen Collection Privacy Issues

- No undressing and gowning
- No pocket searches without cause
- No medication inquiries
- Private enclosure for urination
- “Monitored” collection

Collection Security Issues

- Wrapped collection container.
- Wrapped specimen bottle(s).
- Specimen always in donor’s sight.

- Donor signature and initials obtained after specimen bottle is sealed.
- Specimen bottle(s) CoC form secured until sealed in shipping container.
- Restricted access to shipping container.
- Always keep collection bottle in sight of donor.

Direct Observation

- Collector must notify site supervisor or employer representative.
- Observation by same-gender individual.
- Direct observation noted in remarks section.
- Limited to special circumstances.

Direct Observation Criteria Required

- Specimen temperature out of range (90–100°F):
 - Offer body temperature measurement.
- Tampering attempt observed:
 - Donor conduct or specimen qualities.
- Send suspect specimen to laboratory.
- Use new CoC and kit for witnessed collection.

Direct Observation Criteria Optional

- Previous specimen dilute (SG < 1.003, low urine creatinine, < 20 mg/dL).*
- Compared to next collection opportunity.
- Previous specimen canceled as unsuitable
- Re-collection of specimen required.
- Return-to-duty or follow-up tests.

* Decision about direct observation made by employer

Shy Bladder

- Provide up to 40 oz. of fluids at collection site to provide urination.
- Provide up to 3 hours to urinate.
- Discontinue collection attempt after 3 hours.

- Report to employer as shy bladder.
- Refer donor for medical evaluation by employer-designated physician.

Split Specimens Collection

- Mandatory for Federal Highway Administration (FHWA), Federal Aviation Administration (FAA), Federal Transit Administration (FTA), and Federal Railway Administration (FRA) supervised industries and companies.
- Collect 30 mL for primary specimen, 15 mL for split specimen.
- No combination of voided specimens.
- Subdivide specimens at collection site.
- Use 7-part CoC on each specimen bottle.
- Ship bottles + 3 copies of the CoC to lab for testing of primary.

Goals for a Forensic Urine Drug Testing Laboratory

- To discriminate reliably between those specimens that contain drug or its metabolite at or above the cut-off and those that do not.
- To do this in a legally defensible manner.

Initial Test (Screening Test)

- An immunoassay screen used to eliminate “negative” urine specimens from further consideration should have high sensitivity.
- The initial test shall use an immunoassay that meets the requirements of the U.S. Food and Drug Administration (FDA) for commercial distribution.

Negative Specimen

- Any specimen whose apparent concentration of drug or metabolite is less than the preestablished cut-off concentration for that drug or metabolite.
- NOT necessarily a specimen containing no drug or metabolite.

Positive Specimen

- Any specimen whose apparent concentration of drug or metabolite is greater than or equal to the preestablished cut-off concentration for that drug or metabolite.

What Is the Cut-Off?

- An arbitrary point on a continuum of possible drug or metabolite concentrations.
- Used to divide specimens into negatives and positives.
- Methods of estimating will vary according to immunoassay used.

Mandated Cut-Offs (ng/mL)

- Marijuana metabolites – 50
- Cocaine metabolites – 300
- Opiate metabolites – 2000*
- PCP – 25
- Amphetamines – 1000

*25 ng/mL if immunoassay is specific for free morphine

Confirmatory Test

- A second analytical procedure used to confirm the identity of a specific drug or metabolite which is independent of the initial test and which uses a different technique or chemical principle from that used in the initial test. Most commonly used technique is gas chromatography/mass spectrometry. Confirmatory tests must have high sensitivity.

Confirmation Cut-Offs (ng/mL)

- Marijuana metabolites – 15
- Cocaine metabolites – 150
- Opiate metabolites – 2000
- PCP – 25
- Amphetamines:
 - Amphetamine – 500
 - Methamphetamine – 500

Unexpected Methamphetamine Issues

- Conversions of large amounts of ephedrine and ephedrine-containing over-the-counter (OTC) pharmaceuticals to methamphetamine during gas chromatography/mass spectrometry confirmation.
- No conversion to methamphetamine's metabolite, amphetamine.
- Reporting rule: Specimens must contain at least 500 ng/mL of methamphetamine and at least 200 ng/mL of amphetamine to be reported positive for methamphetamine.

Other Gas Chromatography/Mass Spectrometry Procedures

- Identify 6-mono-acetylmorphine (6-MAM): The initial metabolite of heroin
- Differentiate the *d*- and *l*-stereoisomers of methamphetamines: Vicks Inhaler® contains the *l*-stereoisomer of amphetamine (*l*-stereoisomer = legal stereoisomer).

Adulteration/Dilution Testing

- Specific testing not presently required under guidelines
- Creatinine reported as <20 mg/dL.
- Specific gravity reported as <1.003.
- Presence of adulterant must be “forensically validated.”
- *In vivo* adulteration/dilution.
- *In vitro* adulteration/dilution.

In Vivo Adulterants

- Ingested water (most common adulterant)
- Ingested herbals — used most commonly to mask THC
 - Golden seal — to mask THC (yellow root)
 - Herbal teas
 - “Test Pure”
 - “THC Free”
- Oral diuretics
- Chemicals
 - Vinegar
- Vitamin C

In Vitro Adulteration

- Definition: The addition of a substance to a urine specimen for the purpose of altering drug testing results.
- Most commonly used adulterants:
 - “Freeze Dried Urine” urinaid (bleach)
 - “Urine Acid” (gluteraldehyde)
 - “Mary Jane’s Super Clean 13” (crystal clear soy)
 - “Urine Luck Plus” (concentrated HCl)
 - “Klear” (oxidizing agent—potassium nitrite)
 - “Stealth”
 - Many other unknown urine adulterants

Contents of a Typical Litigation Package

- Chain of custodys (external and internal)
- Immunoassay data (specimens, calibrators, controls)
- Gas chromatography/mass spectrometry data (specimens, calibrators, controls)
- Reports (electronic, certified Chain of Custody)

Interception of Negative Urine Drug Test Results

- No drug use?
- No drug use recently?
- Urine dilution and/or adulteration?
- Creatinine as a marker (<20 mg/dL)?
- Specific gravity as a marker (<1.003)?
- Urinaid, bleach, Mary Jane Super Clean, Golden Seal tea, diuretics, used as *in vitro* adulterants?
- Drug present, but below preestablished cut-off level?

Interpretation of Positive Urine Drug Test Results

- Indicates use only?
- Does not correlate with impairment?
- Does not indicate route of administration?
- Cannot tell time of use or amount of use?

Unique Screening Characteristics of Commonly Abused Drugs

Cannabinoids

- 61 cannabinoids in marijuana.
- delta-9-Tetrahydrocannabinol (THC) is the psychoactive constituent.
- 11-NOR-THC-9-carboxylic acid is the major metabolite in urine.
- Have at least 20 other oxygenated metabolites, including hydroxylated compounds, other monocarboxylic acids, and dicarboxylic acids.
- Pattern of metabolites may depend on type of user

Cannabinoids Issues

- Passive inhalation
- Unknown digestion — “Seedy Sweeties” hemp seeds
- Time since last use
- Release from lipid depots
- Degradation post-collection

Cocaine

- Metabolites in humans: benzoylecgonine and ecgonine methyl ester are major metabolites. Norcocaine is a minor metabolite.
- Cocaine’s plasma half-life is very short; that of benzoylecgonine is much longer.
- Benzoylecgonine can be detected for days after use.
- Urine concentrations of benzoylecgonine can be extremely high (100,000s of ng/mL).
- Preferred routes of administration: smoking, snorting and injection.
- Oral route reported to be ineffective but!
- Therapeutic uses: Ear–Nose–Throat (ENT) surgical procedures and Tetracaine–Cocaine–Adrenalin (TAC) solution for open wound instillation and topical anesthesia for suture repair of lacerations.

Cocaine Issues

- Passive inhalation
- Unknown ingestion

- Degradation post-collection
- Herbal teas (e.g., Health Inca Tea, “HIT,” decocted teas from Columbia)

Opiate Metabolism

Morphine

- Major metabolite of heroin
- Also a metabolite of codeine
- Constituent of opium
- Routes of administration of heroin: Injection, snorting, and smoking
- Therapeutic uses of morphine: Many, including narcotic analgesics

Codeine

- Metabolites: Morphine and norcodeine.
- Codeine concentrations during use can be in the 10,000s of ng/mL; morphine concentrations are significantly lower.
- Therapeutic uses: Many, including narcotic analgesics and antitussives.

Opiate Issues

- Codeine vs. Morphine: After use, concentrations of morphine and codeine similar late in the excretion curve. Morphine may be higher than codeine. Latter can be lower than cut-off and therefore reported as negative.
- Synthetic opiates (e.g., hydrocodone, hydromorphone) cannot be detected and reported.
- 6-MAM as a marker of heroin use:
 - Concentrations very low, particularly after single use, and half-life very short.
 - Infrequently detected in workplace programs.
 - If 6-MAM absent, need “clinical signs of opiate abuse” for a positive-use test.
- Poppy Seeds
 - Morphine present in poppy seeds, amount dependent on geographical origin.
 - Urine morphine concentration can be found in the thousands of ng/mL, usually in the hundreds.
 - Codeine usually very low, often cannot be detected.

- Poppy Seeds: General Guidelines
 - Concentration of morphine greater than 5000 ng/mL suggests use of heroin (or opium), particularly when codeine concentrations are much lower.
 - High codeine concentrations (>300 ng/mL) with morphine to codeine ratios less than two generally rule out poppy seed ingestion.
- Remember presence of 6-MAM indicates heroin use!

Amphetamines

- Only ones that can be reported: methamphetamine and amphetamine.
- Amphetamine is a metabolite of methamphetamine.
- Excretion is pH dependent, an acidic urine enhances excretion.
- In U.S., methamphetamine generally represents the abused form of the drug. In Europe, amphetamine is more commonly abused.
- Methamphetamine routes of administration: injection, snorting, smoking (“ice”), and oral.
- Both still used therapeutically.

Amphetamine Issues

- Metabolites of other preparations, e.g., benzphetamine, p-chlorobenzphetamine (Ascetin® from Mexico), and selegeline (as the l-isomers).
- Isomers of methamphetamine: l-isomer in Vicks Inhaler®. Can be differentiated from psychoactive d-isomer by gas chromatography/mass spectrometry.
- Immunoassays detect other sympathomimetics, e.g., ephedrine, pseudoephedrine, and phenylpropanolamine, often at only very high concentrations. Can be differentiated by gas chromatography/mass spectrometry.
- Temporary reporting rule for methamphetamine (at least 500 ng/mL of methamphetamine, plus at least 200 ng/mL of amphetamine as methamphetamine metabolite).
- Methamphetamine still very much a Western U.S. issue.
- Designer amphetamines (Ecstasy, Eve): MDMA, MDA, and MDE: generally regionalized. Cannot be detected and reported.

PCP

- No legitimate use
- Excretion pH dependent. An acidic urine enhances excretion
- Normally smoked
- Regional use patterns

Other Drugs

- Barbiturates: Urine positives almost always butalbital and phenobarbital.
- Benzodiazepines: Oxazepam common metabolite of several; most labs focus on this one metabolite. Gas chromatography/mass spectrometry methods not in common use for several “newer” benzodiazepines, including alprazolam. Xanax® (Alprazolam) most commonly prescribed one today.
- Methadone and methaqualone: Very few (if any) positives.
- Other drugs not a real issue in the workplace.
- Specific “workplaces” have their own problems (e.g., athletics—anabolic steroids, anesthesiologists—fentanyl).

Other Specimens

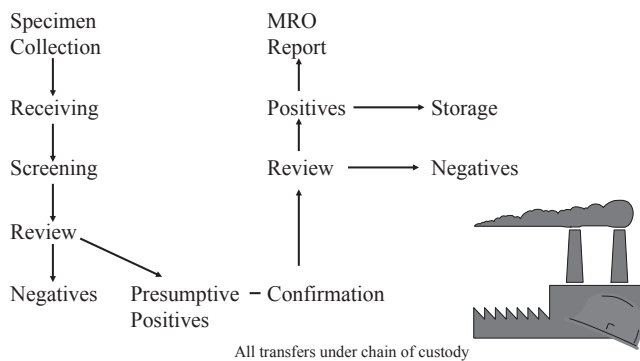
- Blood: Not routinely used, may be collected post-accident or for alcohol.
- Saliva: Little information on drug detection. Proposed as a specimen for alcohol.
- Hair: Still not widely accepted. Difficult to confirm marijuana use because of technology limitations. Also major questions re: contamination (particularly cocaine).
- Breath: Accepted only for alcohol testing.

Forensic Laboratory Drug Testing Laboratory Selection Questions

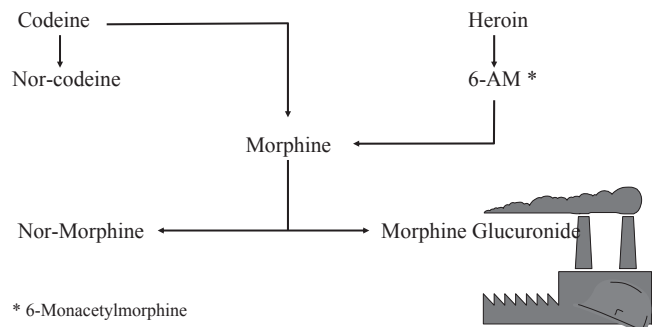
- Is the laboratory licensed and/or accredited to perform drug analyses?
- What drugs are included in the screening test(s) and the confirmation test(s)?
- What is the cost of testing?
- What is the turnaround time?
- Is a chain of custody procedure available?

- What supplies (urine containers, etc.) are provided?
- What is the laboratory's report mechanism and how is confidentiality ensured?
- How long can positive specimens be stored at the laboratory?
- Can the laboratory offer support (technical testimony) at hearing or in court-related cases?

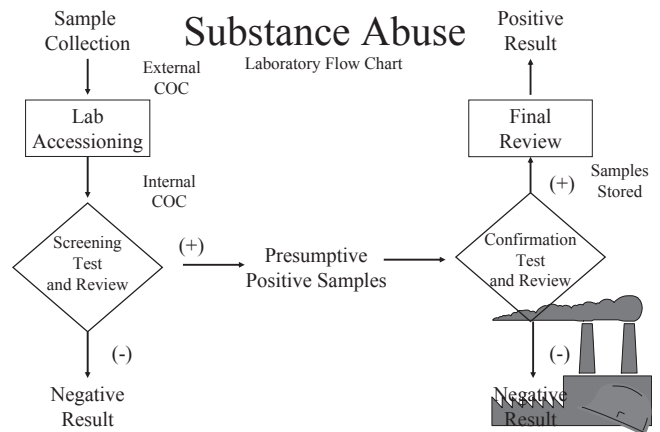
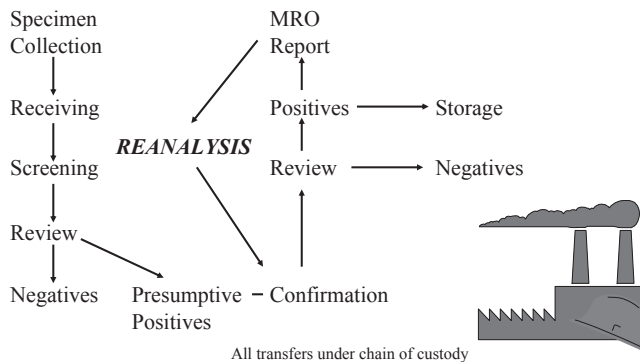
Substance Abuse The Laboratory Chart Flow



Substance Abuse Opiate Metabolism



Substance Abuse The Laboratory Flow Chart



MRO Responses

Medical Miranda

- “The reason I am speaking to you personally is because the results of your urine drug test have been received and it is a positive test. The purpose of this interview is to provide you with an opportunity to voluntarily share information with me that might explain a positive result, such as anything from your medical history, prescriptions, recent treatment or something in your diet. Before I ask you any further questions, I want to tell you that any information that you may disclose will be TREATED CONFIDENTIALLY and not be released unless a U.S. Department of Transportation regulation requires or permits such a disclosure. You have the option of not discussing the matter with me, if you choose. Do you have any questions at this point?” Non-contact positive test donor declines interview — refuses medical interview — report as positive drug test.

5-Day Non-Contact Positive

- Verified positive results without donor interview.
- Document that donor knew to call MRO.
- 14-day non-contact positive.
- Document efforts to contact donor.
- Report as “subject to further review?”

Specimen Not Suitable

- Medical review interview procedure similar to positive test interview.
- MRO’s duty is to ascertain if an acceptable explanation exists for the specimen’s unsuitability.
- Declare final, verified, results accordingly.
- Re-collection under direct observation.

Amphetamine Interpretation

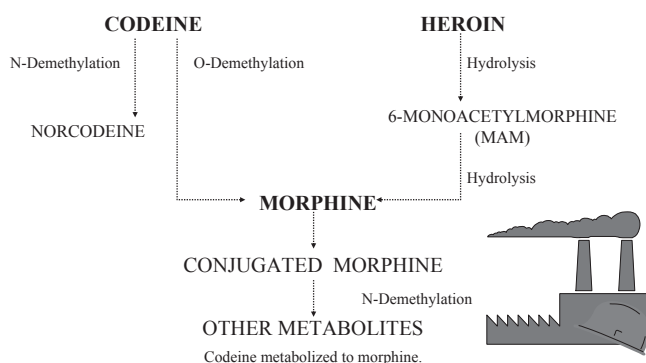
- Not as difficult as it may seem.
- Remember d and l isomers of methamphetamines are the key (d “drug” and l “legal” amphetamines not at issue — exception is selegiline).
- 200 ng/mL or more of amphetamine must be present to report a methamphetamine positive result.
- <500 ng/mL amphetamine won’t be reported.
- Know your laboratory - isomers by request?

Opiate Interpretation

- Clinical evidence of unauthorized use of an opiate (burden of proof on the MRO).
- Verify prescriptions — codeine and morphine only.
- Old prescription?
- Spouse’s prescription?
- Foreign preparations?
- Unexplained result with no admission of use and urinary findings of:
 - low morphine only
 - morphine and codeine
 - codeine only
 - high morphine levels
- Perform physical examination.
- Poppy seed ingestion (alone) rarely will produce morphine in excess of 2000 ng/mL; morphine/codeine 2:1 or more.
- 6 mg heroin (IM) produces peak morphine level of 8721 ng/mL.

Substance Abuse

The Drugs of Abuse



- 20 mg morphine (IM) produces peak urinary concentration of 18,000 ng/mL.
- 60 mg IM codeine produces peak urinary excretion of 15,682 ng/mL codeine.
- Morphine peaked at 3096 ng/mL following cocaine ingestion (both codeine and morphine peaked at 2.8 hours).
- At 36 hours, morphine remained reportable (491 ng/mL) while codeine was not (207 ng/mL).
- Codeine in body converted to morphine → morphine sulfate + morphine glucuronide.
- Also cancel if specimen is unavailable, inadequate for testing, or untestable.
- Report cases where donor request for split test results in cancellation on standard form.
- Do not cancel test if collector failed to mark split not collected.
- MRO must request split test in writing.
- MRO can order primary re-analysis: Donor can request split-specimen analysis (for drug only).

Return to Work Determination

Opiate Interpretations — Rules of Thumb

- Poppy seeds are usually not responsible for urinary opiates 24–36 hours after ingestion.
- Morphine/codeine ratios of less than 2-3:1 usually rule out poppy seed ingestion as the sole source for urinary opiates (suggest codeine use).
- Morphine levels over 1–2000 ng/mL without reportable codeine or over 4–5000 ng/mL with codeine reported usually rule out poppy seed ingestion as the sole source for urinary opiates.
- Low morphine levels only (<2000 ng/mL) can be found with poppy seed ingestion, the “tail end” of a codeine ingestion, or several days after morphine or heroin use.
- Very high levels of morphine (>10,000 ng/mL) with little or no codeine almost always mean heroin or morphine use.
- A finding of 6-MAM in the urine is specific evidence of heroin abuse.

Split Sample Issues

- Splits optional for two operating administration, RSPA and USCG.
- MRO’s responsibility to offer split test.
- Regulations moot on financial responsibility for split sample testing.
- Request for split should not delay reporting of result to employer.
- Donor must request split within 72 hours.
- Lab will not routinely report lack of split sample availability.
- Failure of split to confirm initial test result requires cancellation of report to DOT.

- Clearance by MRO necessary for USCG and RSPA.
- USCG requires statement related to “cure.”
- FAA asks for statement of drug “dependence or non-dependence.”
- MRO should evaluate all clinical information; interview donor.

Shy Bladder Evaluation

- Required after failure to produce an adequate urine sample (45mL/30mL).
- MRO may perform evaluation.
- MRO may receive information from outside physician evaluator and transmit to employer.
- Examination must develop pertinent data that might explain the donor’s inability to produce a sample.
- Evaluation may consist of:
 - Medical history (renal diagnosis, output problems)
 - Medication history (anticholinergics, anti-hypertensives, antihistamines)
 - General physical (turgor, orthostatic changes)
 - Simple lab tests (U/A, BUN, creatinine)
 - Cystoscopy, IVP usually not needed
- Written report required
- DOT July 25, 1995 Notice defines “medical condition” (for shy bladder purposes) as an “ascertainable physiologic condition (e.g., urinary system dysfunction) as distinct from assertions of ‘situational anxiety’ or unsupported claims of dehydration.”

Table 25.8 Medical Review Officer's Conclusions in Complex Opioid Cases

Urinalysis	Employee Presents Prescription	Claims Poppy Seed Eating	Signs of Abuse	MRO's Conclusion of Probable Explanation
1. 6-Monoacetylmorphine with or without other findings	NR	NR	NR	Urinary confirmation of heroin abuse
2. Morphine	Morphine	NR	NR	No urinary confirmation of opioid abuse
3. Morphine	None	Yes	Yes	Urinary confirmation of heroine abuse
4. Morphine predominates, some codeine	Morphine	NR	None	No urinary confirmation of opioid abuse
5. Morphine predominates, some codeine	Codeine	No	Yes	Urinary confirmation of morphine or heroin abuse
6. Morphine predominates, some codeine	Codeine	Yes	NR	No urinary confirmation of opioid abuse
7. Codeine predominates, some morphine	Codeine	NR	NR	No urinary confirmation of opioid abuse
8. Codeine predominates, some morphine	None	Yes	Yes	Urinary confirmation of codeine abuse
9. Codeine predominates, some morphine	None	Yes	None	No urinary confirmation of opioid abuse

Note: NR = Not relevant.

Table 25.9 Atypical Specimens

Laboratory Research	MRO and Employer Action
1. Specific gravity < 1.003 and creatine < 0.2g/L	The MRO can, but is not required to, inform the employer that the specimen's specific gravity is less than 1.003 and its creatinine is less than 0.2g/L (20 ng/mL). Given this information, the employer can, but is not required to, direct that the donor's next urine drug test specimen be collected under direct observation.
2. Specimen not suitable	The MRO attempts to determine the reason for the specimen's unsuitability. If the specimen remains "not suitable" and the reason remains unclear, the MRO reports the test as "test not performed" and advises the employer that another specimen should be collected immediately and under direct observation.
3. Specimen adulterated: presence of <adulterant> detected	The MRO reports the outcome as "test not performed" and notifies the employer that the specimen was adulterated. An adulterated specimen is considered a refusal to submit to testing.

Note: All figures are Power Point-drawn self-explanatory diagrams to be inserted into test and do not require separate captions.

Epidemiological Design and Statistical Analysis of Toxicological Investigations

Epidemiological Design: Outline

Definitions

Disease natural history and prevention levels

- Disease stages
- Prevention levels

Causation

- Intrinsic causation
- Extrinsic causation
- Models of causation

Rates

- Rates
- Definitions
- Some considerations

Data Sources

- Data sources for denominators
- Threats to study designs

Descriptive Epidemiology

- Person — who?
- Place — where?
- Time — when?

Analytical Epidemiology

- Observational studies
- Interventional studies

Experimental Epidemiology

- Confounding

Screening

- Targets for screening

Surveillance

- Life tables

Definitions

- Epidemiology: The study of the distribution and determinants of diseases and injuries in human populations based on the frequencies and types of illnesses and injuries in populations and the risk factors that influence their distribution.
- Scope of epidemiology:
 - Epidemic: The occurrence of a group of illnesses in a group or community of similar nature in excess of normal expectancy. Pandemic = worldwide epidemic.
 - Endemic: The constant presence of an illness in a group or community within a given geographic area. Example: rabies is endemic in raccoons in Ohio.
- Stages of disease:
 - Susceptibility = behavioral > genetic = risk factors
 - Presymptomatic = pathogenesis = premalignant (premorbid)
 - Clinical disease = morphological extent. Example: cancer = tumor, nodes, metastases TNM classification. Functional classification = Example: New York Heart Association Classification (NYHA I–IV) of impairment by cardiovascular disease
 - Disability = residual = short (Acute) or long term (Chronic)

Disease Natural History and Prevention Levels

Disease Stages

- Susceptibility
- Presymptomatic
- Clinical disease
- Disability

Prevention Levels

- Primary: Primary prevention of disease by vaccination or behavioral change (smoking cessation).
- Secondary: Screening for presymptomatic disease to prevent exacerbations and complications.
- Tertiary: Treatment of clinical disease.
- Quaternary: Rehabilitation to restore functional capability and quality of life.

TABLE 26.1 Disease and Prevention

Disease Stage	Prevention Level	Examples
Susceptibility	Primary	Immunization
Presymptomatic	Secondary	Pap smear
Clinical disease	Secondary	TAH — cervical cancer
Disability	Tertiary	Physical therapy, pain management

Causation

• Intrinsic Causation

- Host factors
- Specific immunity
- Herd immunity
- Personality traits — Type A or B

Extrinsic Causation

- Biological — zoonotic
- Social — cultural
- Physical environment

Models of Causation

- Interrelational (ecologic)
- Epidemiologic triangle
- Web of causation
- Wheel of man and environment
- Ecologic fallacy

Rates

Rates

Rate = numerator =
number of cases of events \times time period

Denominator = population at risk

- Estimate midyear population
- Excludes diseased persons (except for large population)
- Requires a period of observation:
 - Census year
 - Attack rate = incidence rate over a period that spans entire epidemic

Definitions

- Rate: A proportion that includes a specification of time. Example: cancer deaths/100,000/year.
- Ratio: Relationship between two numbers. Example: X:y, odds 1:10, odds ratio 1.8.
- Proportion: A type of ratio in which the numerator is included in the denominator and expressed as a percent (%). Example: males:all births.
- Basic rates:
 - Incidence rates (new disease)
 - Prevalence rates (existing disease)
- Special rates:
 - Crude rates
 - Proportions and specific rates
 - Adjusted ratios

Basic Rates

Incidence rates (over a period of time)
= number of new cases of a disease \div population at risk

Prevalence rates (at a point in time)
= number of existing cases of a disease \div total population

Some Considerations

Incidence

- Requires a health status measure
- Requires a date of onset
- Numerator = persons diseased
- Denominator = population at risk:

Incidence Density: Person — Time Denominator

- Used when diseased persons are observed for unequal periods of time due to death or attrition.
- Use is valid under three conditions only:
 - Risk of disease or death is constant throughout period.
 - Rate of disease or death is same among those observed and those lost to follow-up.
 - For rapidly fatal diseases — inflates incidence rates by adding to numerator and subtracting from denominator.

Prevalence

- Point prevalence:
 - Denominator includes entire population
 - Used in cross-sectional surveys due to ease and low costs.
 - Favors chronic over acute diseases.
- = Existing cases at a point in time \div Total population
- Period prevalence:
 - Denominator includes entire population.
 - Preferred for mental illness because date of onset is difficult to determine.
 - Favors chronic over acute diseases.

= Existing cases during period.

Average population

Incidence & prevalence

Person	D	J	F	M	A	M	J	J	A	S	O	N	D
1													
2													
3													
4													
5													
6													
7													
8													
9													
10													

Special Rates

- For total populations:
 - Crude rates — Example: crude birth rates
- For population subgroups:
 - Specific rates — Example: age-specific death rate, males, ages 25–34
 - Adjusted rates — Example: standardized mortality rate (SMR)

Crude Rates

- Definition: Summary rates based on the actual number of events (births, death, diseases, etc.) in a total population over a given time period.
- Expressed as a % (per 100), per 1000 (births), or per 100,000 (deaths).
- Do not account for subgroup differences in risk. Example: Total population is an inappropriate denominator for births that occur only in females.

Specific Rates

- Definition: Subgroup rates specific for age, sex, race, or other demographics variables.

- Age-specific death rate (26–34):
= no. of deaths among 25–34 year olds.
Average 25–34-year-old population

Adjusted Rates

- Definition: Summary rates statistically transformed to remove the effects of demographic differences in populations. Adjustments are often made for age, sex, race, smoking status, etc., due to their confounding effects on morbidity and mortality.
- Adjustment methods:
 - Direct: Specific rates from two or more study populations are applied to a standard population.
 - Indirect: More stable rates of a larger population are applied to the smaller population study groups. Example: SMR = observed (deaths) / expected (deaths).

Proportionate Mortality Ratio (PMR)

- Definition: The relative importance of a specific cause of death in relation to all deaths in a population.
- Ratio not rate — denominator is deaths, not population at risk.
- Permits estimate of lives to be saved by intervention. Example: smoking cessation.

PMR = no. of deaths secondary to a given cause in a specified time period $\times 100\% \div$ total deaths in same time period

Sources of Error in Measuring Rates

- Random error — prevented by randomization:
 - Sampling variability
 - Nonrandom sampling
 - Misclassification
 - Chance events

TABLE 26.2 Comparison of Direct and Indirect Adjustment

	Direct Adjustment	Indirect Adjustment
Data used from standard population	Age distribution	Age-specific rates
Data used from each study group	Age-specific rates	Age distribution
Result of adjustments for each study group	Age-adjusted rate	Ratio of observed to expected deaths (SMR)

- Bias (systematic error) — prevented by experimental design:
 - Self-selection (volunteers)
 - Healthy worker effect
 - Nonresponse (nonparticipation)
 - Inter (intra)-observer bias
 - Recall bias
 - Interviewer bias
 - Illness behavior
 - Treatment bias

Data Sources

Data Sources for Denominators

- Census: Conducted every 10 years since 1790; State Metropolitan Statistical Areas (SMSAs) developed in 1949 and include:
 - 50,000 + urban residents
 - 100,000 + total population
 - Adjacent suburbs
- Vital statistics:
 - National Center for Health Statistics (NCHS)
 - National Death Index (NDI)
 - National Health and Nutrition Examination Survey (NHANES)
 - Hospital and doctor records
 - HMO records
 - Disease registries (Surveillance, Epidemiology, and End Results [SEER] — a federally mandated national cancer registry)

Threats to Study Designs

- Bias: A systematic deviation from the truth:
 - Selection
 - Information
 - Measurement
- Validity: A clear representation of meaning and intent:
 - Measurement
 - Study

Types of Bias

- Selection bias:
 - Volunteers
 - Maturation effects
 - Healthy worker effects
 - Hawthorne effects
 - Institutionalized controls
 - Misclassification
 - Cross-overs
- Information bias:
 - Recall and response bias
 - Nonresponse bias
 - Attrition or study dropouts
 - Lost-to-follow-up
 - Ascertainment bias
 - Conceptual bias
 - Detection bias
 - Interviewer bias
 - Reporting bias
 - Publication bias
- Measurement bias:
 - Instrumentation bias
 - Interpretation bias
 - Intra-rater bias
 - Inter-rater bias
 - Observer bias
 - Presentation bias
 - Sampling bias
 - Lead-time bias
 - Length-time bias

TABLE 26.3 Sampling

Method	Advantage	Disadvantage
Random	One selection bias	Random number table
Systematic	Easy, similar to random	Sequence ordering could resemble study variability
Paired	Good matching for age, sex, SES	More than one control needed, one similarity, spurious associations

Screening Tests Biases

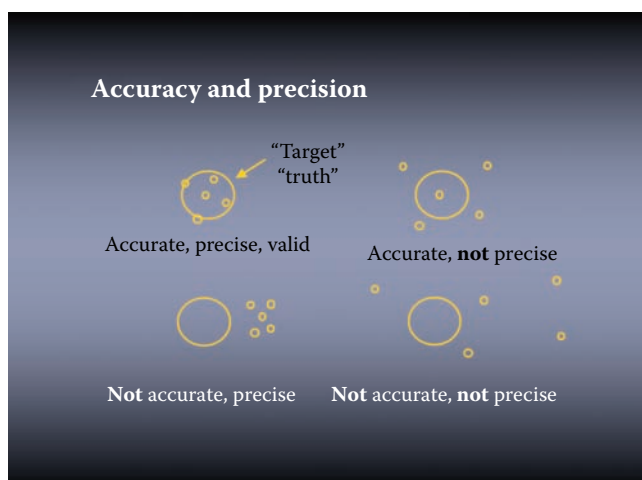
- Lead-time bias: Early diagnosis leads to an erroneous conclusion of improved outcome (survival). Can be accounted for.
- Length-time bias: Longer-lasting diseases are more likely to be detected by screening. Cannot be accounted for.

Validity and Reliability

- Validity:
 - Ability of test to measure the “truth”
 - Composed of sensitivity and specificity
 - Includes content, construct, criterion (gold standard) validity
- Reliability:
 - Precision, reproducibility, repeatability
 - Exists within test, within person, within lab, etc.
 - Assess with kappa statistic
- Both validity and reliability are inherent to test and independent of disease prevalence

Types of Validity

- Face validity
- Construct validity
- Content validity
- Criterion validity:
 - Concurrent validity
 - Predictive validity
- Internal validity:
 - Study design
 - Hypothesis testing



- External validity:
 - Generalizability to the larger population at risk

Measurement Validity

- Face validity: It is what it is. Example: “walks like a duck.”
- Content validity: Measurements represent the underlying concepts.
- Construct validity: Measurements agree with the underlying theories.
- Criterion validity: Measurements are the true “gold standards.”

Types of Criterion Validity

- Concurrent validity: The criterion and measurement occur at the same point in time. Example: infection with fever.
- Predictive validity: The measurement accurately predicts the criterion outcome. Example: MCAT and medical school admission.

Threats to Validity

- Internal threats: Are there elements of the study that can confuse observed treatment effects?
 - Maturation: growth, development, aging, atrophy.
 - History: Experiential learning.
 - Testing: Learning through testing.
 - Instrumentation: Measurement bias.
 - Mortality: Attrition rate.
 - Regression to the mean: Large samples are normally distributed.
 - Recall and nonresponse bias.
 - Confounding: Third variable distorts true relationship between predictions and outcomes.
 - Effect — Modification: Usually age and sex are the most common effect modifiers.
 - Secularization: Long-term trends (exercise) can change outcomes.
- External threats: Can one generalize the results of this study to other similar situations?
 - Testing: Learning through pretesting.
 - Volunteerism: Selection bias.
 - Mortality: “Drop-outs.”

- Hawthorne effects: Observation bias — experimental subjects know when they are being observed and adjust their behaviors.
- Power and sample size.
- Healthy worker effects: Those healthy enough to work have better health outcomes than retirees and the disabled.
- Misclassification.
- Ascertainment bias: Outcomes questionable.
- Cross-over subjects.
- Non-randomization.

Descriptive Epidemiology

Person — Who?

- Age: J-shaped death curve, neonatal deaths and deaths in the elderly.
- Sex:
 - Death: Male > female
 - Morbidity: Male > female
- Race
 - Death: African American > Caucasian
- Socioeconomic Status (SES)
- Occupation
- Marital status
 - Divorced
 - Widowed
 - Single
 - Married
- Maternal age:
 - Down's Syndrome
- Paternal age:
 - Schizophrenia

Place — Where?

- South:
 - Melanoma
- North:
 - Multiple sclerosis
- Southwest:
 - Coccidioidomycosis

- Urban:
 - Sexually transmitted diseases (STDs)
 - Hepatitis C
 - Tuberculosis
- Rural:
 - Anthrax
 - Brucellosis

Time — When?

- Secular trends:
 - Stomach cancer decreasing
 - Pancreatic cancer increasing
- Cyclic changes:
 - Deaths: Winter > summer
 - Arthropod-borne (ARBOR) infectious diseases: Summer > winter
 - Melanoma: Summer > winter
 - Hepatitis A: Winter > summer
 - Motor vehicle accidents: Weekends > weekdays
- Epidemics (national)
- Pandemics (international)

Analytical Epidemiology

Observational Studies

- Nonexperimental studies:
 - Cross-sectional studies
 - Case-control studies
 - Cohort studies:
 - Prospective studies
 - Retrospective (historical) studies

Interventional studies

- Experimental studies
- Randomized controlled trial (gold standard)
- Quasi-experimental studies:
 - Before and after studies

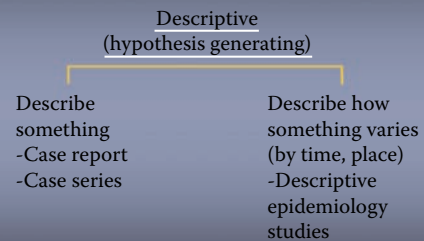
Cross-Sectional Study

- Population sample:
 - Bad outcome, exposed group (a)
 - Good outcome, exposed group (b)
 - Bad outcome, not exposed group (c)
 - Good outcome, not exposed group (d)
- Advantages:
 - Quick
 - Cheap
 - Gives prevalence
 - Generates hypotheses
- Disadvantages:
 - Statistically inefficient
 - No time sequences
 - Cannot test hypotheses
 - Based on prevalence, not incidence

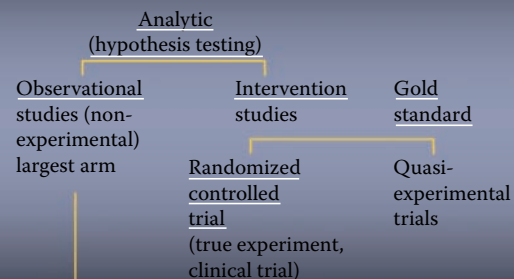
Case-Control Study

- Population sample:
 - Exposed group (a) — bad outcome
 - Not exposed group (c) — bad outcome
 - Exposed group (b) — good outcome
 - Not exposed group (d) — good outcome
- Advantages:

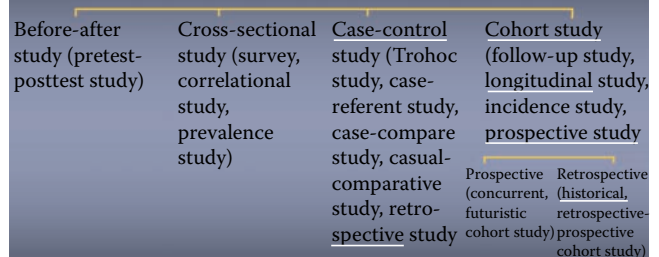
Overview diagram of research designs



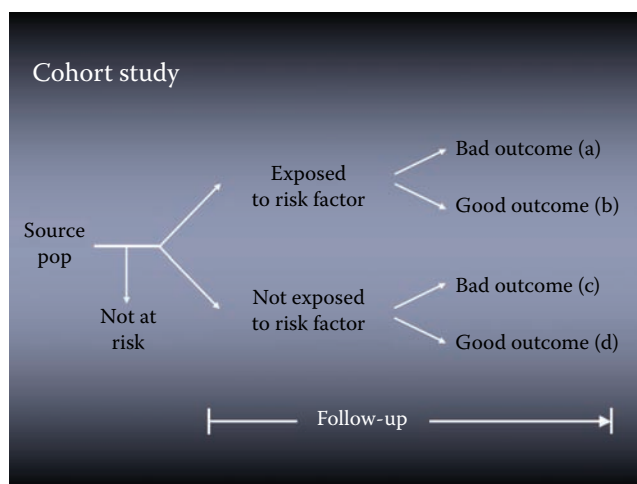
Overview diagram of research designs



Overview diagram of research designs



- Rare cases well studied
- Frequent exposures
- Long latency periods
- Identifies risk factors
- Generates hypotheses
- Quick and cheap
- Few subjects needed
- Disadvantages:
 - Cannot determine incidence rates
 - Retrospective rates
 - Cannot test hypotheses
 - Misclassification bias
 - Poor controls
 - Volunteers
 - Selection bias
 - Healthy worker effects
 - Disease behaviors
 - Recall bias



- Treatment bias
- Detection (diagnosis) bias
- Confounding — 3rd variables

Analyzing Case-Control Studies

Sources of Bias

- Selection bias:
 - Volunteers
 - Institutionalized controls
 - Healthy worker effects
 - Maturation
- Information bias:
 - Misclassification
 - Recall and response bias
 - Interviewer bias

Cohort Study

- Advantages:
 - Determines incidence rates
 - Good for rare exposures
 - Determines true relative risk
 - Identifies multiple outcomes
- Disadvantages:
 - Time-consuming
 - Expensive, resource-intensive
 - High attrition rates
 - High lost-to-follow-up rates
 - Many subjects required

TABLE 26.4 Analytical Epidemiology: 2 x 2 Table

Disease or exposure of interest	Outcome	
	Bad	Good
Yes	a	b
No	c	d

TABLE 26.5 Analyzing Case-Control Studies Odds Ratio

Cases	Controls	
	Disease	No Disease
Exposed	a	b
Not Exposed	c	d

Odds Ratio = ad/bc = Estimate of Relative Risk

TABLE 26.6 Analyzing Case-Control Studies Relative Risk

Cases	Outcomes	
	Disease	No Disease
Exposed	a	b
Not Exposed	c	d

Relative Risk = $[a/(a+b)]/[c/(c+d)]$

Sources of Bias

- Selection bias:
 - Differential exposures
 - Healthy worker effects
 - Misclassification
- Information bias:
 - Detection bias
 - Nonresponse bias
 - Lost-to-follow-up
 - Attrition

Cohort Studies

- Advantages:
 - Fast and cheap
 - Logistically simple
 - Requires few subjects
 - Good for rare exposures
- Disadvantages:
 - High lost-to-follow-up rates
 - High attrition rates
 - Very small sample sizes
 - Misclassified exposures
 - Misclassified outcomes
 - Past confounders unapparent

Analyzing Retrospective Cohort Studies

$RR = \text{incidence rate among exposed} = [a/(a+b)]$
 $\text{Incidence rate among unexposed} = [c/(b+d)]$
 Same as for Prospective Cohort Studies = $[a/(a+b)] / [c/(b+d)]$

Randomized Controlled Trials (RCTs)

- Advantages:
 - Requires random assignment
 - Eliminates selection bias
 - Tests hypotheses
 - Permits blinding of subjects and observers (double blinding) and analysis (triple binding)
 - Strong internal validity
- Disadvantages:
 - Expensive
 - Time-consuming
 - Blinding difficult
 - Cross-overs occur as subjects switch to treatment groups with better outcomes
 - Weak external validity
 - Low power secondary to small samples

Quasi-Experimental Studies

- Before-and-after studies
- Nonequivalent control group studies

Criteria for Causal Association (Bradford-Hill Criteria)

- Association should be strong ($RR > 2.0$).
- Association should be consistent.
- Association should exhibit a dose-response relationship.
- Exposure should precede the outcome temporally.
- Association should be biologically plausible.
- Association should be supported by animal and other human studies.

TABLE 26.7 Retrospective Cohort Study

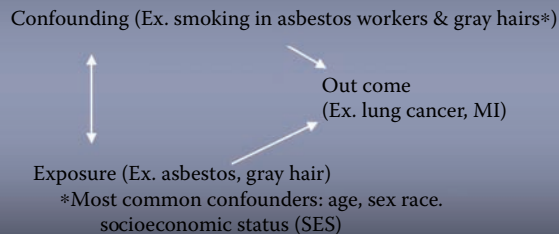
Past		Present		Future
Subjects assembled according to past exposures	←	Identify cohort from the past		
	→	Determine outcomes now	→	Determine outcomes again later

TABLE 26.8 Bias in Observational Studies

Type of Misclassification	Effect on Odds Ratio or Relative Risk
Exposed cases as controls	Underestimate
Exposed controls as cases	Overestimate
Exposed cases as unexposed	Underestimate
Exposed controls as unexposed	Overestimate
Unexposed cases as controls	Overestimate
Unexposed controls as cases	Underestimate
Unexposed cases as exposed	Overestimate
Unexposed controls as exposed	Underestimate
Nonsystematic misclassification	Underestimate

Experimental Epidemiology

Confounding definition



- Confounder is associated with the exposure, but not a result of exposure.

Detecting Confounding

- Demonstrate that confounder is associated with both exposure and outcome.
- Adjust for confounding in study analysis. If there is a difference between adjusted and unadjusted results, then suspected confounder is a true confounder.

Eliminating Confounding

- Remove by design:
 - Randomization
 - Restriction of entry
 - Excluding criteria
 - Matching
- Remove by analysis:
 - Stratification
 - Rate adjustment
 - Compare subjects with bivariate analysis (t-tests)
 - Account for confounders with multivariate analysis (ANOVA)

Confounding

Confounding Definition

- Confounding: The distortion of the true relationship between an exposure and an outcome resulting from a mutual relationship with one or more extraneous factors that can either account for or mask the true relationship.

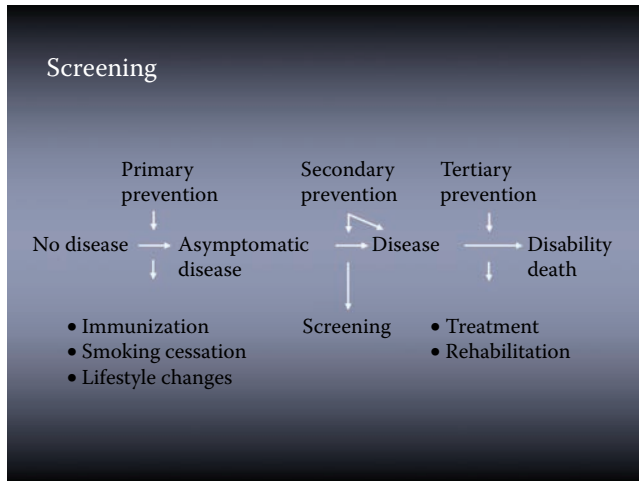
Criteria for Confounding

- Confounder is associated with the outcome:
 - Confounder is an actual risk factor for outcome.
 - Confounder affects likelihood of recognizing outcome.

TABLE 26.9 Selecting Controls

Control Group	Advantage	Disadvantage
General population	Matching by county	↓ Response rate
Hospital patients	Available, cooperative	Already sick, ↓ confounding
Spouses and siblings	Similar SES and environment	Male:Female, large families, no siblings, genetically similar, effect modification
Case associations	Similar + healthy, same lifestyle + SES	Too similar, response rate, recall bias

Screening



Targets for Screening

- The disease is significant and important.
- The disease has a long asymptomatic stage.
- There are reliable screening tests for the disease.
- Treatment of asymptomatic disease improves outcomes.
- Access exists to sufficient resources for diagnosis and treatment of the disease.
- Benefits of screening for the disease should outweigh the benefits of other programs.

TABLE 26.10 Screening Tests: True Disease

The Test	The Truth	
	Disease	No Disease
Disease (+)	a (TP)	b (FP)
No Disease (-)	c (FN)	d (TN)
	Sensitivity = $a / (a+c)$ = TP / all disease	Specificity = $b / (b+d)$ = TN / all no disease

TABLE 26.11 Screening Tests: True Disease

The Test	The Truth	
	Disease	No Disease
Disease (+)	a (TP)	b (FP)
No disease (-)	c (FN)	d (TN)
		PPV = $a / (a+b)$ = TP test / all P tests NPV = $c / (c+d)$ = TN test / all N tests

TABLE 26.12 The 2x2 Table: Diagnostic Tests

Test Results	Disease Status		
	Disease	No Disease	
Positive	a	b	a + b
Negative	c	d	c + d
	a + c	b + d	Total
Sensitivity = $a / a + c$			
Specificity = $d / b + d$			
PPV = $a / a + b$			
NPV = $d / c + d$			

TABLE 26.13 Screening Test

↑ Prevalence →	↑ PPV + ↓ NPV
↓ Prevalence →	↓ PPV + ↑ NPV
↑ Sensitivity →	↑ NPV
↑ Sensitivity →	↑ PPV

Screening Tests

$$\text{Prevalence} = \frac{a + b}{a + b + c + d} \text{ or,}$$

$$P = a + b \div a + b + c + d$$

$$= \frac{\text{TP} + \text{FN}}{\text{TP} + \text{FP} + \text{FN} + \text{TN}} \text{ or,}$$

$$P = \text{TP} + \text{FN} \div \text{TP} + \text{FP} + \text{FN} + \text{TN}$$

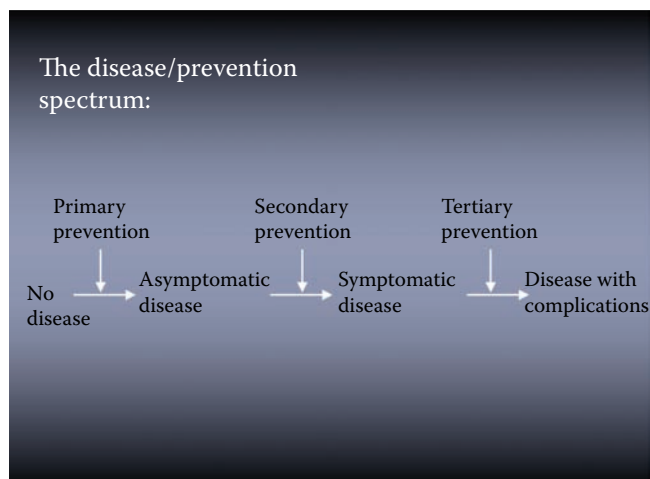
$$= \frac{\text{Prevalence of all disease}}{\text{Whole Population}} \text{ or}$$

$$P = \text{Prevalence of all disease divided by whole population}$$

Screening Tests Biases

- Lead-time bias:
 - Early diagnosis leads to an erroneous conclusion of improved outcome (survival). Can be accounted for.
- Length-time bias:
 - Longer-lasting diseases are more likely to be detected by screening. Cannot be accounted for.

Screening and Screening Strategies



Surveillance

- Active surveillance:
 - Periodic data collection
 - Regular interval sampling
 - Environmental (vector) sampling
 - Food services inspection
 - Health facilities inspection
- Passive surveillance
 - Unsolicited reporting
 - Required disease reporting
 - Tumor registries
 - Vital registries
 - Required lab reporting

Life Tables

Current life table

Cohort life table

Follow-up life table

Current Life Tables

- How age-specific death rates affect a population, adjusting for premature death.
- Characteristics: age intervals, age-specific death rates, number living, number dying, remaining life [years of productive life lost (YPLL)].

Cohort Life Tables

- The actual historical record of a group (e.g., cancer patients).
- Provides 1- and 5-year survival rates to assess treatment effectiveness.

Follow-Up Life Tables

- How long do I have left to live?
- Provides for chronic disease registries (e.g., cancer and cardiovascular diseases).

Biostatistics for Epidemiology: Outline

Probability

- Likelihood ratios
- Probability rules
- Binomial distribution

Descriptive statistics

- Types of data
- Summary analysis
- Variation
- Distribution

Differential statistics

- Testing for trends
- Hypothesis testing
- Rates, proportions, and associations
- Cohort studies
- Case-control studies
- Error and power

Probability

Likelihood Ratios

Probability = no. of ways events can occur;
no. of equally likely events that can occur

Probability Rules

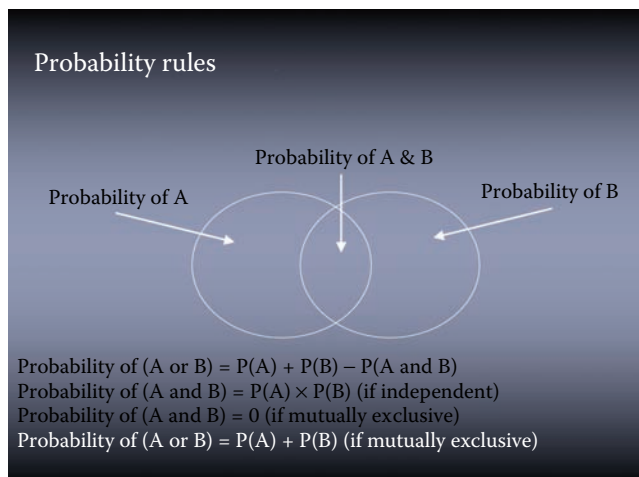
- Multiplication Rule = $P(A \text{ and } B) = P(A) P(B)$
 - (both A + B)
- Conditional Probability = $P(A/B) = P(B) \cdot P(A/B)$
 - (A given B)
- Addition Rule = $P(A \text{ or } B)$,
 - (*mutually exclusive*) = $P(A) + P(B)$
- Additional Rule = $P(A \text{ or } B \text{ or both})$
 - (*not mutually exclusive*) = $P(A) + P(B) - P(A) P(B)$

Mutual Exclusivity

- A and B are independent events.
- A and B cannot occur simultaneously.
- A and B are not related.
- Opposite for non-mutual exclusivity:
 - (A and/or B)

Binomial Distribution

- Outcomes are limited to two choices
- Decision tree analysis: Dead or alive, sick or well, treat medically or treat surgically, radiotherapy or chemotherapy
- Decision tree cost-effectiveness analysis
- Marginal cost-effectiveness analysis
- Threshold (break-even) analysis



Descriptive Statistics

Types of Data

- Continuous (interval) data: Measured on an arithmetic scale. Example: height, weight, blood pressure, heart rate, FEV1.
- Nominal (categorical) data: Divided into two (binomial) or more unordered, discrete categories. Examples: sex, race, religion.
- Ordinal data: A predetermined ordering (ranking) of nominal (categorical) data. Example: SES, Likert scale, qualitative and functional scales.

Summary Analysis

Central Tendency

- Mean = average
- Median = middle
- Mode = repeating

Variation

- Range = highest – lowest
- Variance = sum of squared deviations from mean
- Standard deviation = square root of variance

Distribution

Normal Distribution

- Bell-shaped
- Unimodal
- Symmetric about mean, \bar{X}
- Compared to test the null hypothesis (H_0)
- Example: t and z distributions
- Central limit theorem applies
- Central tendency = mean
- SE (\bar{X}): Not applicable
- Variation = $s = \sigma$

Skewed Distribution

- Not bell-shaped
- Often multimodal
- Asymmetric about mean, \bar{X}
- Transformed to test H_0
- Example: F distribution (ANOVA)
- No central limit
- Central tendency = median
- SE (\bar{X}) = SE ($\bar{\mu}$)
- Variation = $s \neq \sigma$

TABLE 26.14 Summary Analysis

Quantity	Sample	Population
Mean	\bar{X}	μ (mu)
Variation	s^2	σ^2 (sigma squared)
Standard deviation	S^a	σ (sigma)
Standard error	SE (\bar{X})	SE (μ)
^a Preferred measure of variation		

The normal distribution

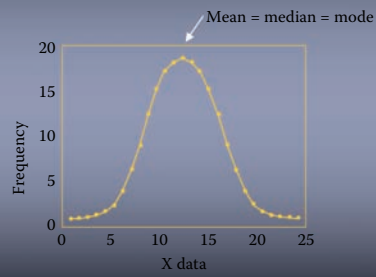
Normal distribution

of distribution

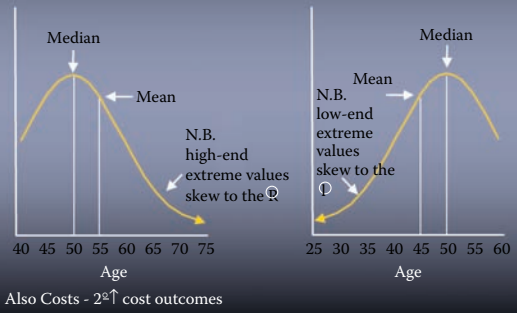
$\mu \pm \sigma = 68.2\%$

$\mu \pm 2\sigma = 95.4\%$

$\mu \pm 3\sigma = 99.6\%$



Skewed distribution



Differential Statistics

Testing for Trends

- Linear regression: How much one dependent (Y) variable increases or decreases on the average as another independent (X) variable changes.
- Multiple regression: How much one dependent variable (Y) increases or decreases on the average as multiple other independent variables (Xs) change. Xs = predictor variables. Us = outcomes.
- Correlation: A measure (r) of the strength of an association.

Trend Variables

- Independent (input): Variable (X) is independent of dependent (outcome) variable; placed on x-axis.
- Dependent (outcome): Variable (Y) is entirely dependent on input variable; placed on y-axis.

Correlation Coefficient (r)

- r = a measure of the strength of linear association between the independent (x) and dependent (y) variables.
- r has no units and takes on values between -1 (strongest inverse relationship) and $+1$ (strongest positive relationship).
- When $r = 0$, there is no relationship between the two variables, $x + y$.
- The stronger a correlation r , the more nearly the regression line y approximates a straight line.
- Regression lines can be compared to test H_0 using the t-test.
- $y = a + bx$ = straight line.

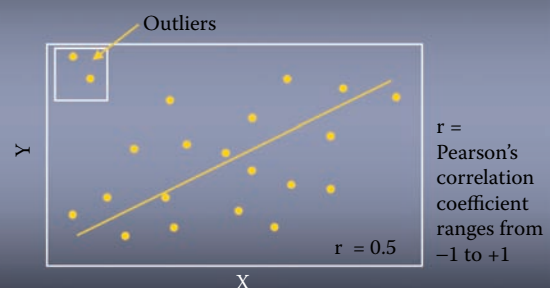
TABLE 26.15 Correlation and Type of Variable

Correlation Coefficient	Variable	Distribution
Pearson product moment (r)	Continuous	Normal
Spearman rank (r_s)	Ordinal	Skewed

Least-squares regression

$$r = \frac{1 - \frac{\text{sum of squared deviations from regression}}{\text{sum of squared deviations from mean}}}{1}$$

The scatterplot



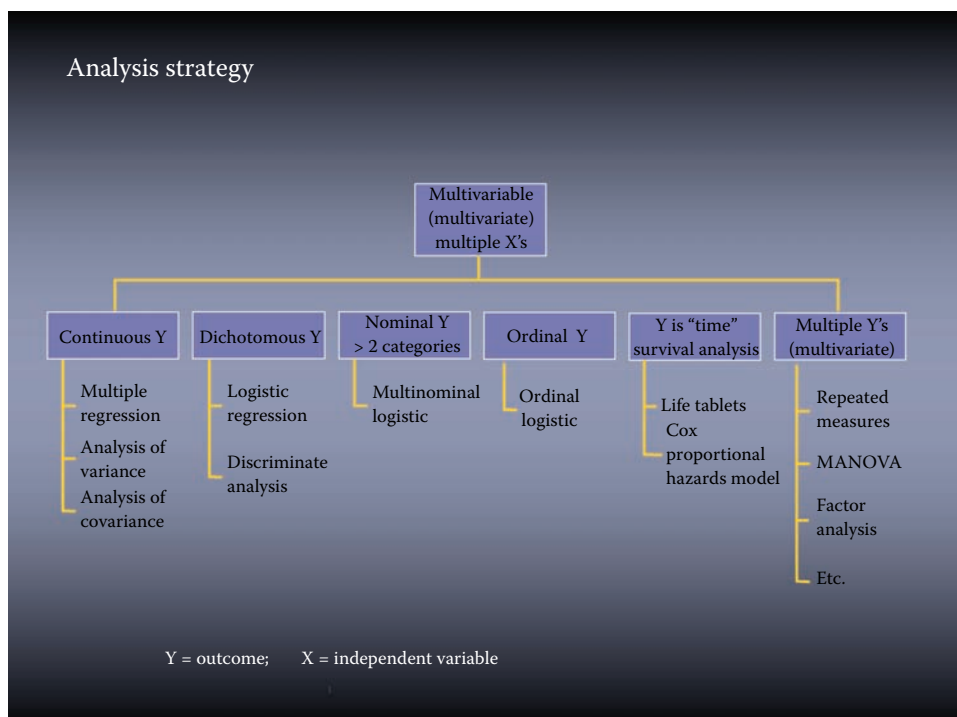
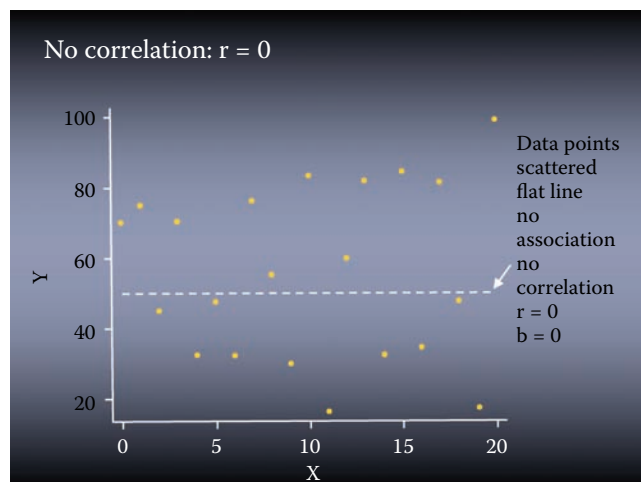
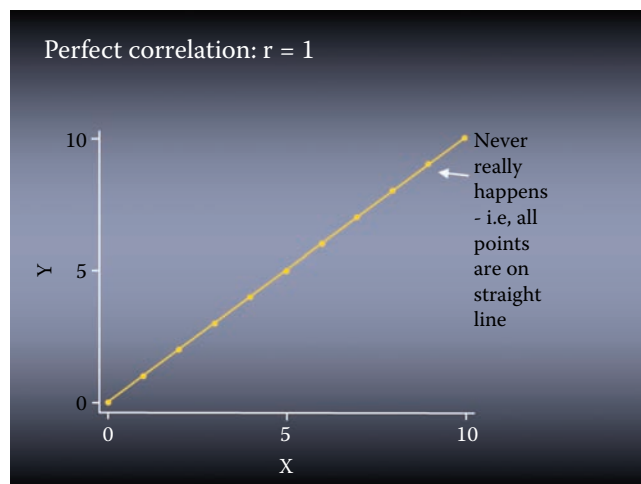


TABLE 26.16 Rough Guide to the Use of Statistical Methods

Dependent Variable	Independent Variables	
	Continuous	Categorical
Continuous	Scatterplot Linear regression	t-tests ANOVA ANCOVA ^a
Categorical	Discriminate analysis	Contingency tables Stratified analysis Logistic regression ^a
Outcome = dependent variable Predictor = independent variable		
^a Special case.		

TABLE 26.17 Differential Statistics Comparative Groups

Date	Two Groups	Three or More Groups
Continuous	t-test (paired vs. unpaired)	ANOVA
Nominal	Chi-square T., McNemar's T.	Chi-square T.
Ordinal	Mann-Whitney T.	Kruskal-Wallis T.

TABLE 26.18 Analytical Investigations in Epidemiology

	Cohort	Case-control	Experimental
Time	Pro/retro	Retro	Pro
Cost	Moderate	Low	High
Disease	Rare	Rare	Common
Compare	Incidence	Prevalence	Outcomes
Measure	RR	OR, X2	Test statistics (T, F)
Control	No	Yes	Yes
Randomize	No	No	Yes
Rigidity	Intermediate	Lowest	Highest
Gold Standard	No	No	Yes

Hypothesis Testing

What Test to Use

- $z \rightarrow$ continuous: Compare sample mean vs. population mean.
- $t \rightarrow$ continuous: Compare two sample means.
- $X^2 \rightarrow$ categorical: Compare two probabilities or percentages from two samples.

Assume the Null Hypothesis (H_0) of No Difference

- Note degrees of freedom based on rows and columns ($df = \{r-1\} \times \{c-1\}$) for X^2 .
- Small test statistics (t, F) indicate H_0 true.
- Large test statistics lead to rejection of H_0 .

Rates, Proportions, and Associations

Chi-Square

- Positively skewed distribution.
- High test statistic values lead to rejection of H_0 .
- Square of difference of observed – expected/expected.
- Expected = computed by proportion of observed on n .
- Less rigidity than continuous comparisons.
- Use the z-test statistic, often with Yates (continuity) correction, $x^2 = z^2$.
- Replace with Fisher's exact test when any expected value is <5 .

Confidence Intervals

- Tell us how close an estimate is to the population parameter.

- An interval of numbers in which we have a specific (95–99%) degree of assurance or confidence that the value of the test parameter was captured.
- Allows investigators to say that 95% (99%) of all sample means from n fall within ± 1.96 (± 2.58) SEs of the population mean.
- Can also be used to test H_s using the t distribution.

Cohort Studies

TABLE 26.19 Epidemiologic Measures of Association

Measure	Study
Relative risk	Cohort study
Odds ratio	Case-control study

Relative Risk (RR)

- The risk of disease in people (study cohort) exposed to a factor relative to the risks in people not exposed (control cohort).
- A measure of the strength of association between an exposure and a disease.
- Requires presentation of data in a 2×2 table.

TABLE 26.20 Relative Risk: 2×2 Table from Cohort Study

	Disease		Total
	Yes	No	
Exposure	a	b	a + b
Nonexposure	c	d	c + d
Total	a + c	b + d	

Relative Risk (RR) Formula

RR = disease rate in exposed = $[a/(a+b)]$.
disease rate in unexposed = $[c/(c+d)]$.

- RR > 1 = Positive association.
- RR < 1 = Negative (protective) association.
- RR = 0 = No association.
- RR > 2–3 = Significant association.

- Formula: $[(a + c)/(a + b + c + d)] - [c/(a+b)] - [c/(c+d)]$ = disease in population attributable to exposure.

Case-Control Studies

Odds Ratio (OR)

Attributable Risk (AR)

- Definition: Incidence in exposed population – incidence in unexposed population.
- Formula: $AR = [a/(a+b)] - [c/(c+d)]$ = disease attributable to exposure.

Population Attributable Risk (PAR)

- Definition: Proportion (%) of disease in a population attributable to an exposure:
 - Total incidence – incidence exposed

- Because disease incidence cannot be calculated in case control studies, RR cannot be calculated.
- OR is an estimate of the RR. Best for rare diseases and widespread exposures.
- OR is a measure of increasing risk of disease from exposure. OR = Risk Ratio.
- Requires presentation of data in a 2×2 table.

TABLE 26.21 Odds Ratio: 2 × 2 Table from Case-Control Study

	Controls	
	Disease	No Disease
Exposed	a	b
Unexposed	c	d

TABLE 26.22 2 × 2 Table: Exposure and Disease

Test Result	Disease Status		
	Disease	No Disease	
Exposed	a	b	a + b
Unexposed	c	d	c + d
	a + c	b + d	Total
Odds ratio = $(a \times d) / (b \times c)$			
Relative risk = $[a / (a + b)] / [c / (c + d)]$			

TABLE 26.23 2 × 2 Table: Matched Pairs

Cases	Controls		
	Exposed	Unexposed	
Exposed	a	b	a + b
Unexposed	c	d	c + d
	a + c	b + d	Total
McNemar's test = b/c = odds ratio			

Odds Ratio Formula

OR = proportion of diseased people in general population = $(a/b) = (ad)$

Proportion of nondiseased in general population = $(c/d) = (bc)$

Error and Power

Error:

Types of error (I, II)

Significance levels (α , β)

P-value

Power:

Relationship to error

Sample size (n)

Effect size (δ)

Error Definitions

- Error types: False positive (I) and false negative (II).
- Significance level (α): P of rejecting H_0 when H_0 is true, or the P of making a Type I error (false positive).
- Significance level (β): P of accepting H_0 when H_0 is false, or the P of making a Type II error (false negative).
- P-value: P of observing a study result by chance alone; should be low ($P < 0.05$) to reject H_0 .

TABLE 26.24 Types of Error

	Type I (False positive)	Type II (False negative)
	Falsely rejecting H_0	Falsely accepting H_0
Definition	Does not exist	Exists
True difference		
Probability	α (1–5%)	β (10–20%)
Significance level	0.01–0.05	0.10–0.20
Power	NA	1– β (80–90%)

TABLE 26.25 Hypothesis Testing: Type I and Type II Errors

Results in the Study Sample	Truth in Population	
	The Means Are Different	The Means Are Not Different
Reject the null hypothesis	Correct	Type 1 α Error
Fail to reject the null hypothesis	Type II β Error	Correct

Power Definitions

- Power: The P of correctly recognizing a true difference or the P of rejecting H_0 when H_0 is false (false negative).
- Power is the complement of β (P of making a Type II error) = $1 - \beta$.
- Power is related to population sample size (N), subject sample size (n), significance level (α), and effect or treatment size (δ).

TABLE 26.26 Power Relationships

Determinants of Power	Effect on Power
$N \uparrow$	\uparrow
$N \downarrow$	\downarrow
$n \uparrow^a$	\uparrow
$n \downarrow$	\downarrow
$\alpha \uparrow$	\uparrow
$\alpha \downarrow$	\downarrow
$\delta \uparrow$	\uparrow
$\delta \downarrow$	\downarrow

^a Power is greatest when there are equal subject numbers in treatment groups.

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COLOR ATLAS OF HUMAN POISONING AND ENVENOMING

JAMES H. DIAZ

The *Color Atlas of Human Poisoning and Envenoming* is the only full-color resource available for the immediate identification of envenoming species, resultant lesions, clinical outcomes, and recommended treatments. Organized in an easily accessible fashion, the atlas offers general information on poisoning management and antidotes. With bulleted text, tables, figure legends, and diagrams, this atlas provides an immediate reference for use in emergency situations.

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